The diagnosis and management of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Mei-Chun Chen, M.D.,Ph. D

Department of plastic and reconstructive surgery

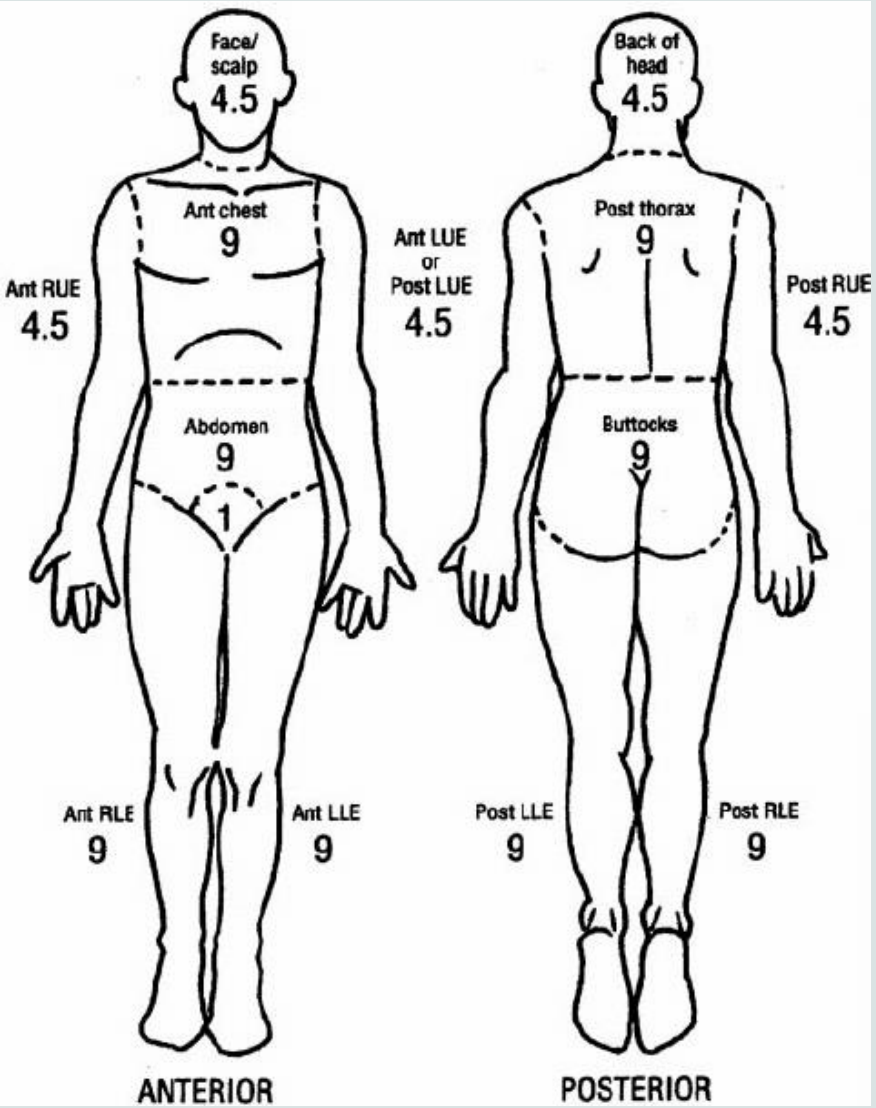
Taipei Veterans General Hospital

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

- Severe muco-cutaneous reactions, characterized by blistering and epithelial sloughing
- SJS and TEN are considered to have the same pathophysiology
- SJS and TEN are classified base on body surface area (BSA) involved

	Body surface area (BSA, %)
Stevens-Johnson Syndrome (SJS)	<10%
SJS/TEN overlap	10–30%
Toxic Epidermal Necrolysis (TEN)	30%

Burn area evaluation (Rule of 9)



Total body surface area, TBSA

- First degree burn is not included
- Head and neck：9 %
- Bilateral upper limb：9 %, each
- Anterior and posterior trunk：18 %, each
- Bilateral lower limb：18 %, each
- Perineum：1 %

- Hand (including fingers)：1%

Incidence of SJS and TEN

- Rare disease
- Reported incidence rates vary by location
- Female predominant (Female : male 1.5:1)

Study	Duration	Location	Incidence (person/per million persons-year)		
			SJS	SJS/TEN	TEN
Frey et al. 2017[1]	1995–2013	United Kingdom		5.76*	
Hsu et al. 2016[2]	2009–2012	United States (adults)	9.2	1.6	1.9
Yang et al. 2016[3]	2009–2013	Korea	3.96–5.03		0.94–1.45
Hsu et al. 2017[4]	2009–2012	United States (children)	5.3	0.8	0.4

* Including SJS, SJS/TEN and TEN

1. J. Investig. Dermatol. **2017**, 137, 1240–1247
2. J. Investig. Dermatol. **2016**, 136, 1387–1397.
3. PLoS ONE **2016**, 11, e0165933
4. J. Am. Acad. Dermatol. **2017**, 76, 811–817.e4.

Mortality of SJS and TEN

Study	Mortality (%)		
	SJS	SJS/TEN	TEN
Hsu et al. 2016[2]	4.8	19.4	14.8
Yang et al. 2016[3]	5.7		15.1
Hsu et al. 2017[4]	0	4	16
Kitami A et al. 2015[5]	3		19
Lim et al. 2016[1]		23.7*	

* Including SJS, SJS/TEN and TEN

1. Burns. 2016 Jun;42(4):836-43.
2. J. Investig. Dermatol. **2016**, 136, 1387–1397
3. PLoS ONE **2016**, 11, e0165933
4. J. Am. Acad. Dermatol. **2017**, 76, 811–817.e4.
5. Jpn J Dermatol 2011; 121: 2467–2482.

Clinical features

- Prodromal symptoms :
  - Fever, malaise, sore throat, and cough
  - precedes the eruption by several days
- Ocular inflammation may also develop before the skin signs
- Cutaneous pain
  - Prominent early feature in SJS/TEN
  - Incipient epidermal necrolysis
- Wide variation in the type of lesion and degree of skin involvement

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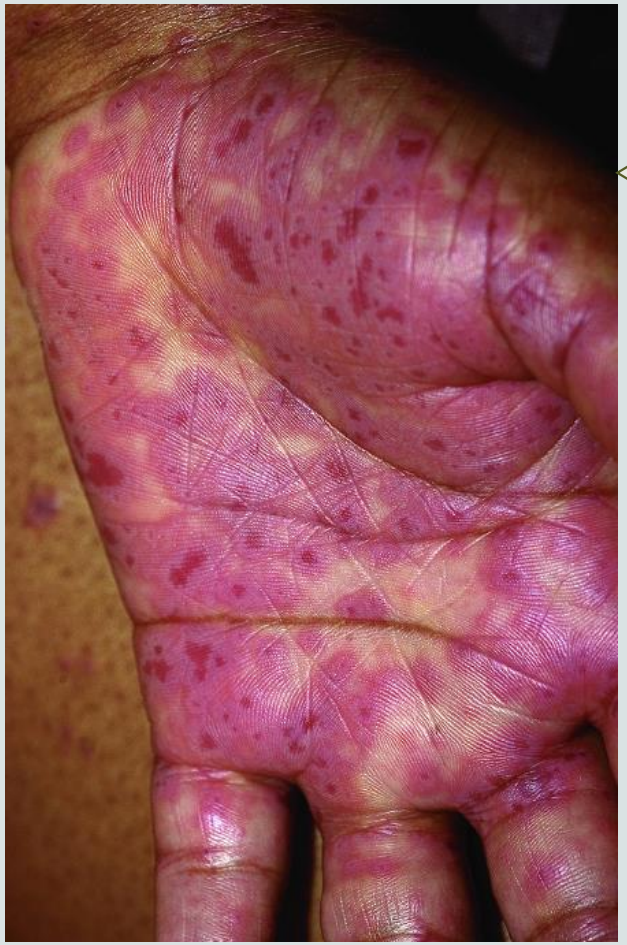
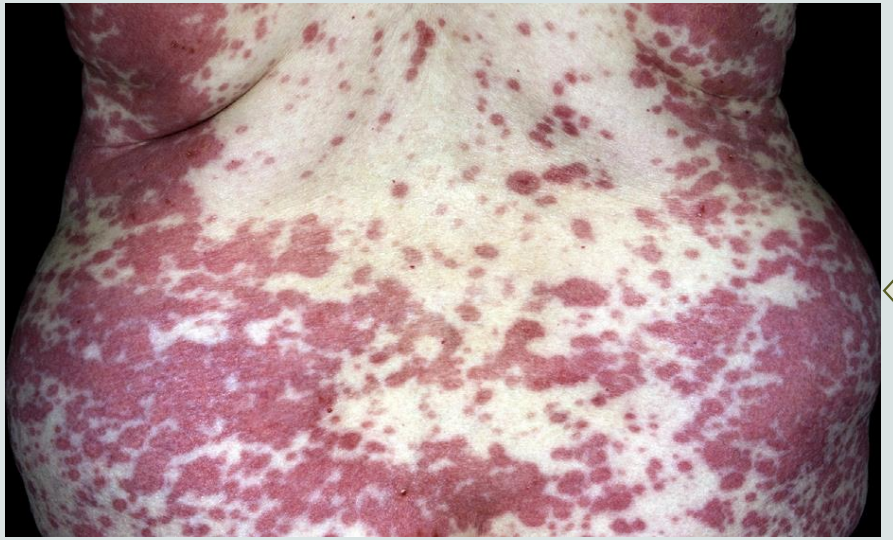
Early skin lesions are atypical targets and/or purpuric macules
Initial involved area : commonly the upper torso, proximal limbs and face.



Atypical targets

- Characterised by a dark red centre surrounded by a pink ring
- In areas, the lesions are confluent



Purpuric macules

- Dark red, flat lesions
- The lesions had joined to produce large areas of dusky erythema over a few days

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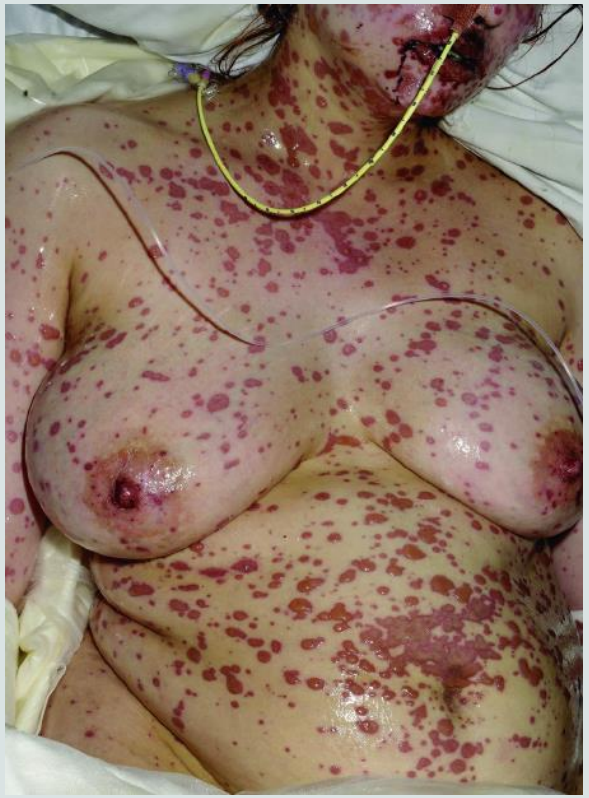
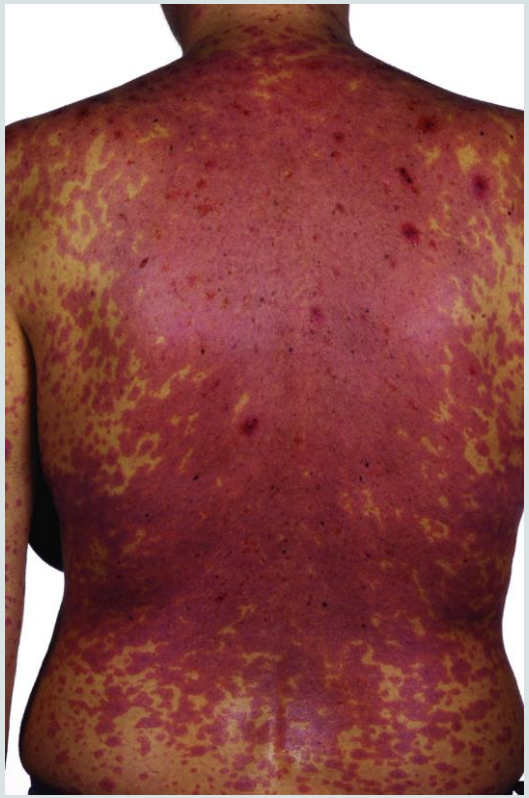
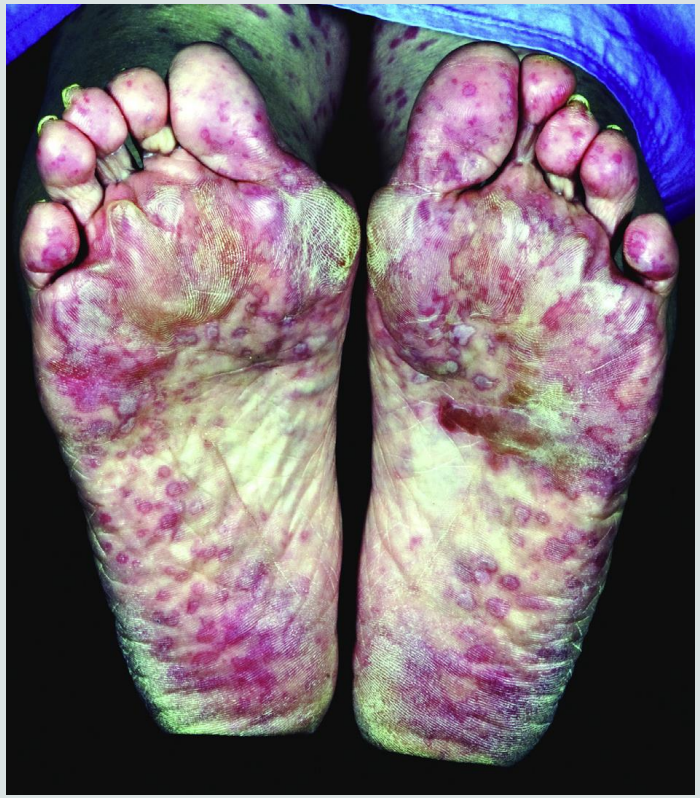
Lesions spread to involve the rest of the trunk and distal limbs
Involvement of the palms and soles is often prominent



Scattered lesions
dusky and blistering lesions on the neck, chest and abdomen



Confluent erythema

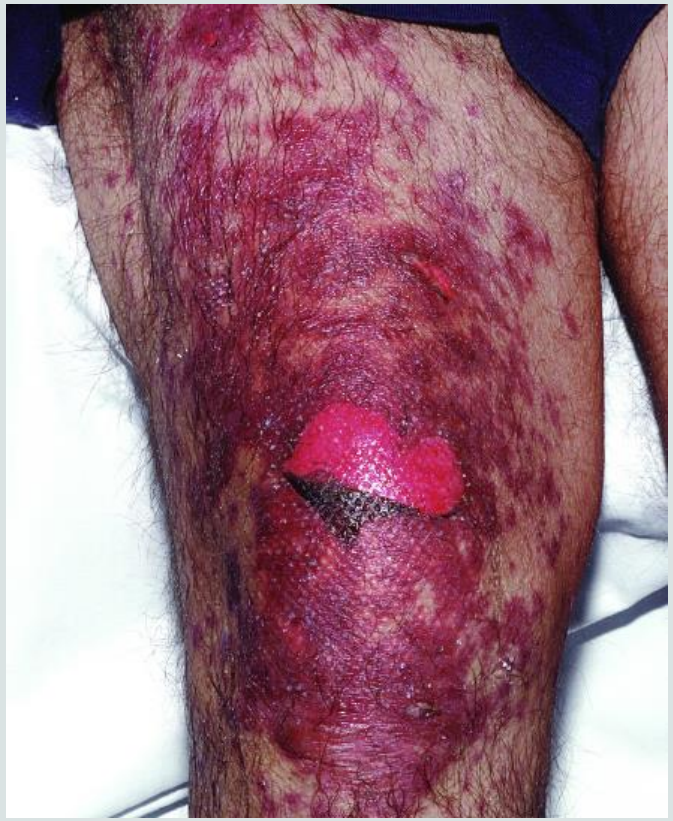


Involvement of palms and soles in SJS/TEN can be prominent and, as at other sites, may blister.

J. Plast. Reconstr. Aesthetic Surg. **2016**, 69, e119–e153

Lesion skin is tender to touch

Nikolsky sign: gentle skin shearing causes lesional, detachable epidermis

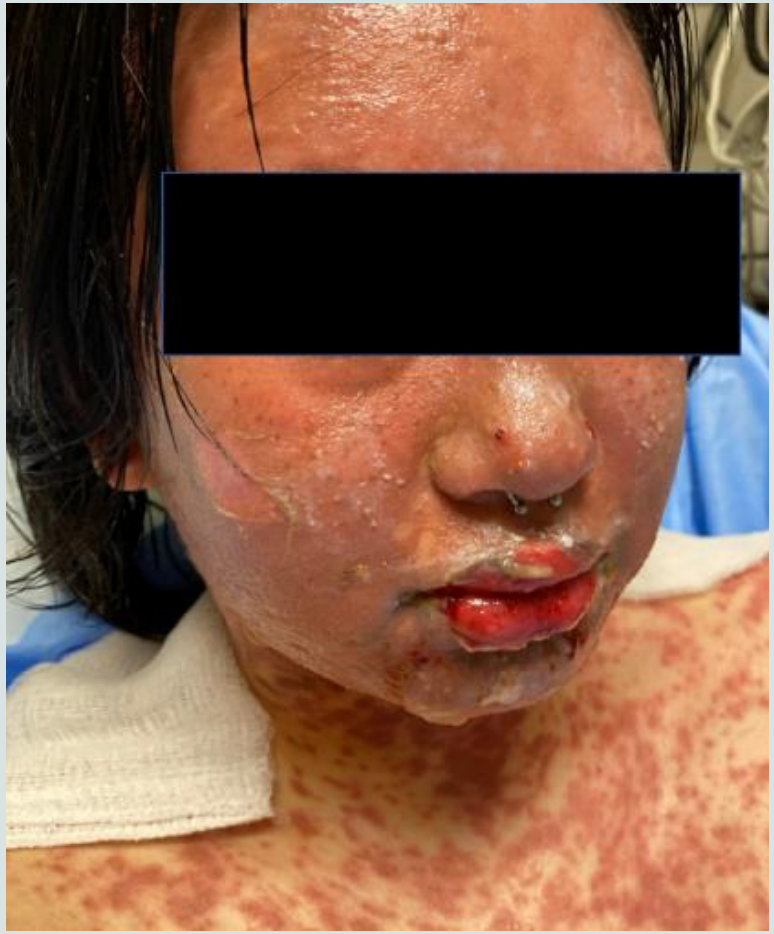


Nikolsky sign

- Nikolsky sign: non-specific
- Epidermal necrolysis: reaching a maximum 5–7 days after disease onset
- Denuded dermis exudes serum, becomes secondarily infected and readily bleeds.

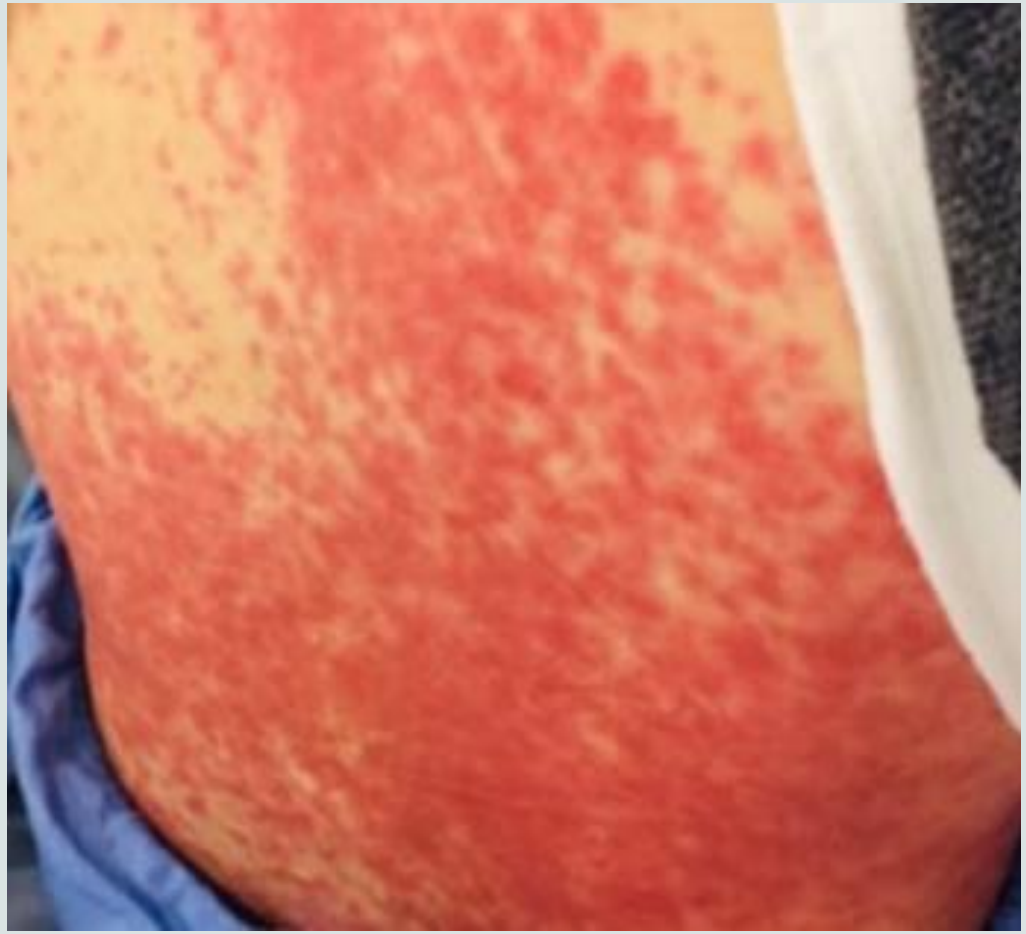
J. Plast. Reconstr. Aesthetic Surg. **2016**, 69, e119–e153

Dusky macules which reach confluence, along with epithelial detachment on the face and lips.



J. Investig. Dermatol. **2016**, 136, 1387–1397.

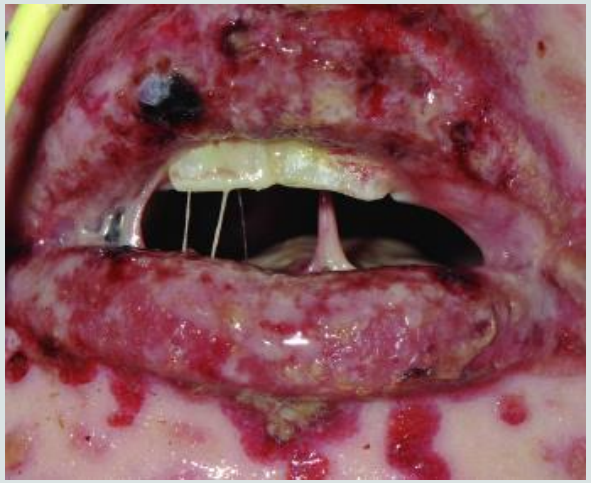
Erythematous macules
Progress to confluent areas of erythema

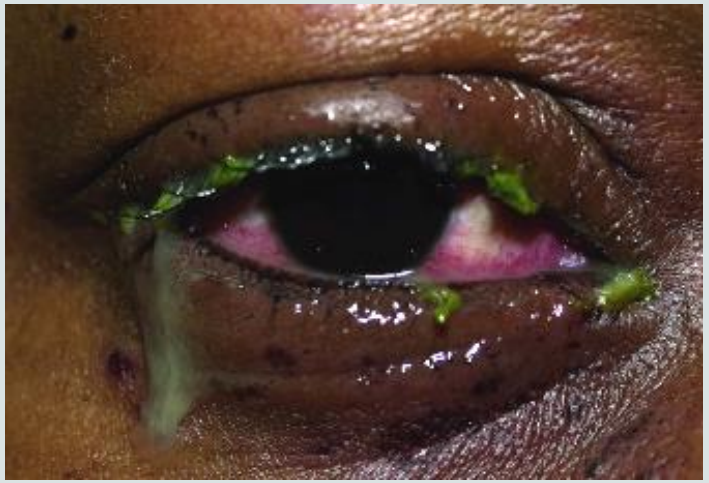


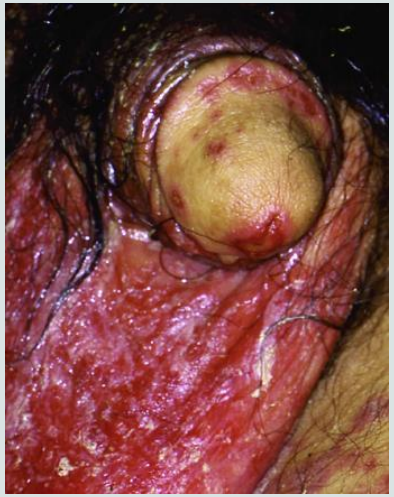
Ther. Adv. Chronic Dis. **2020**, 11

Mucosal involvement of SJS and TEN

- Early feature of SJS/TEN
- 90–100% of cases have oral involvement (mucositis and ulceration)[1]
    - Pharyngeal mucosa is affected in nearly all patients
- 80% of cases have two or more mucosal surface involvement[2]







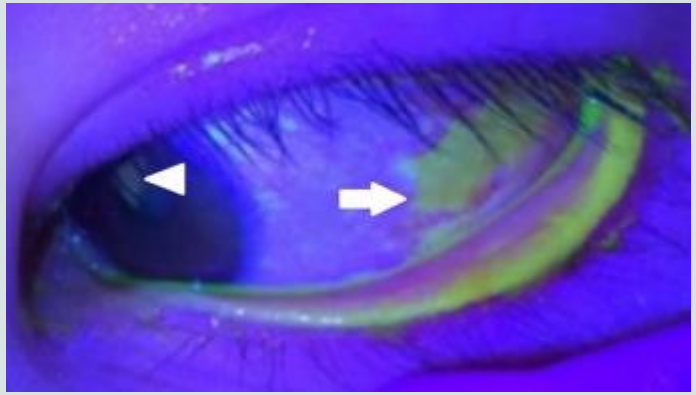
1. Ther. Adv. Chronic Dis. **2020**, 11.
2. J. Investig. Dermatol. **2016**, 136, 1387–1397.
3. J. Plast. Reconstr. Aesthetic Surg. 2016, 69, e119–e153

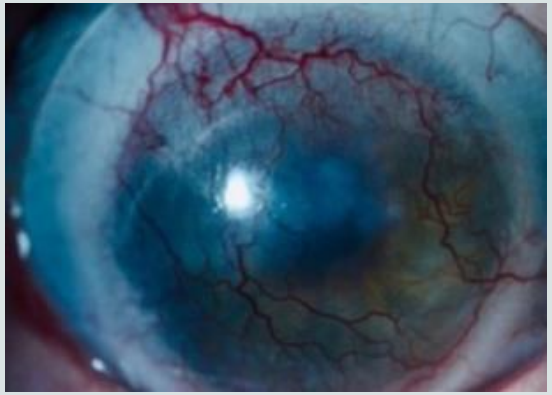
Ocular involvement

- Conjunctival hyperemia to complete epidermal sloughing of the ocular surface
- Early consultation with an ophthalmologist is essential

Acute phase
- Lower eyelid margin skin sloughing
- Conjunctival and corneal epithelial defect

Chronic phase
- Corneal neovascularization

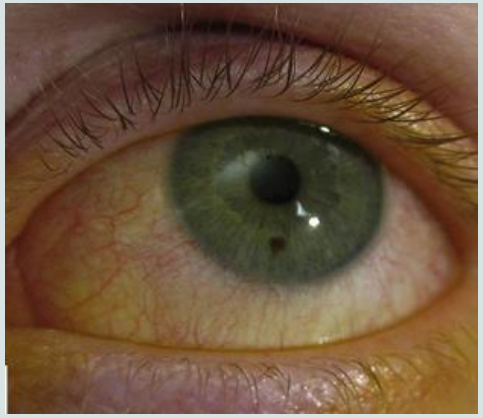
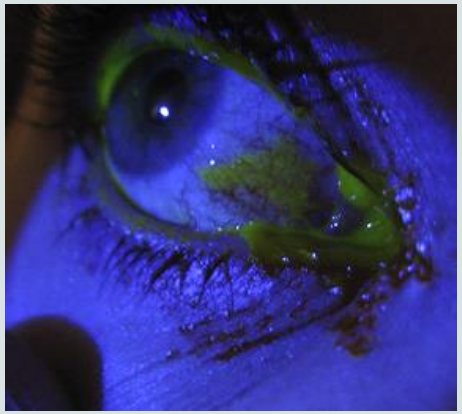
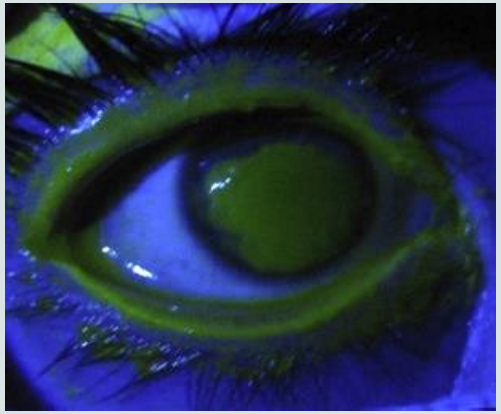
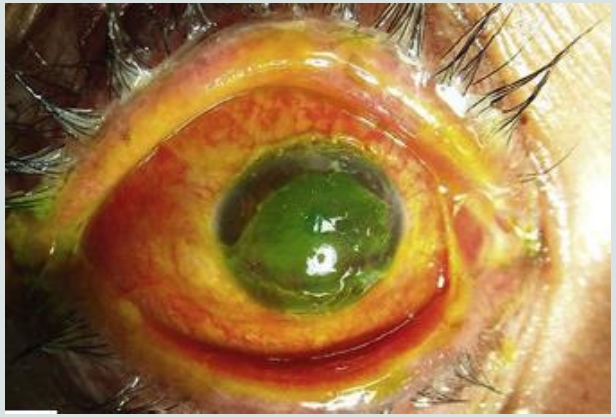




Fluorescein dye illuminated with cobalt blue light

Ophthalmology **2016**, 123, 1653–1658
Ther. Adv. Chronic Dis. **2020**, 11

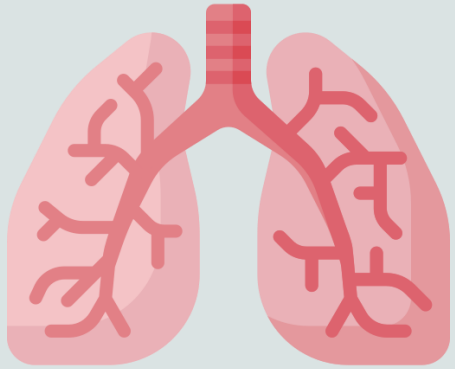
Ocular involvement – Acute phase

Mild	Moderate	Severe	Extreme severe
			

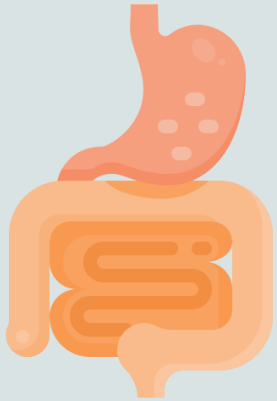
Lid margin	No stain	Stain< 1/3 lid margin	Stain > 1/3 lid margin At least 1 lid	Stain > 1/3 lid margin More than 1 lid
Conjunctiva	hyperremia	No Stain	(+)Stain > 1cm (+)	Stain > 1cm (multiple area)
Cornea	No stain	No Stain	Any epithelial defect more than punctate staining	
Treatment	Medical & close observation		Medical & urgent amniotic membrane transplant	

Ophthalmology **2016**, 123, 1653–1658

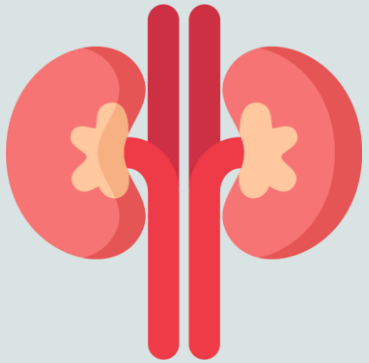
Other symptoms induced by SJS/TEN



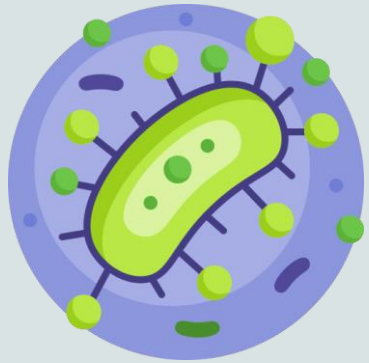
Epithelial necrolysis
Bronchial obstruction
Ventilatory compromise



Epithelial necrolysis
Profuse diarrhea



Hypoperfusion
Acute tubular necrosis
Acute kidney injury



Secondary infection
Sepsis
Major cause of death

. J. Plast. Reconstr. Aesthetic Surg. 2016, 69, e119–e153

Severity of illness score (0–39)

Ocular

Lip/oral

Skin

Oral intake

Malaise

Fever

	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5	Score 6
Ophthalmic lesions							
Pseudomembrane formation	None	Slight pseudomembrane formation	Pseudomembrane is formed but the patient is able to open the eyelids	Difficulty in opening the eyelids	–	–	–
Conjunctival hyperemia	None	Mild conjunctival vascular hyperemia	Moderate conjunctival vascular hyperemia	Severe conjunctival vascular hyperemia	–	–	–
Lip/oral lesions							
Blood crust or hemorrhage or oral erosion	None	Erosion without blood crust or hemorrhage	Erosion with blood crust or hemorrhage on the lip	Erosion with extensive blood crust or hemorrhage on the lip and in oral cavity	–	–	–
Cutaneous lesions							
Effusion in the erosion/ulcer area	Stopped/ none	Slight	Mild	Severe	–	–	–
Hemorrhage in the erosion/ulcer area	Stopped/ none	Mild	Moderate	Severe	–	–	–
Extent of epidermal detachment†	0%	<5%	≥5%, <10%	≥10%, <15%	≥15%, <20%	≥20%, <30%	≥30%
Extent of erythema‡	0%	<10%	≥10%, <20%	≥20%, <30%	≥30%, <40%	≥40%, <50%	≥50%
Cutaneous/mucosal pain	None	Slight pain	Considerable pain	Intolerable pain, requiring sedation	–	–	–
General condition							
Oral intake	Normal	The patient eats more than half	The patient eats less than half.	The patient does not eat meals (including nil p.o. status)	–	–	–
Malaise	None	Mild	Moderate	Severe	–	–	–
Fever	<37.0°C	≥37.0°C, <37.5°C	≥37.5°C, <38.5°C	≥38.5°C	–	–	–

J Dermatol. 2015 Aug;42(8):768-77.

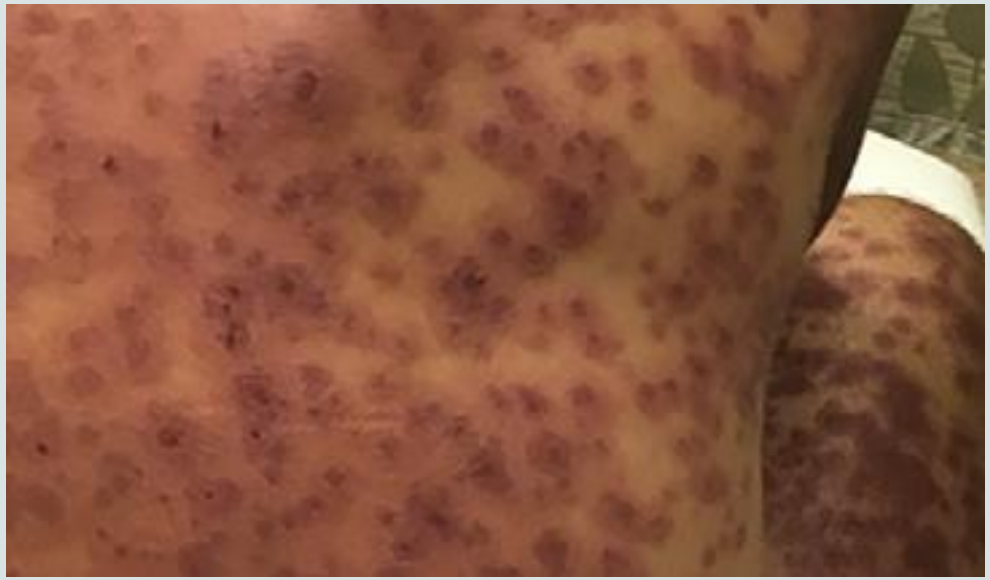
Must differential diagnosis with other desquamating and vesiculobullous dermatoses

Differential Diagnosis of SJS/TEN	
Erythema multiforme major	Pemphigus vulgaris
Staphylococcal scalded skin syndrome	Bullous pemphigoid
Generalized fixed drug eruption (BFDE)	Linear IgA bullous dermatosis
Acute generalized exanthematous pustulosis	Paraneoplastic pemphigus
Phototoxic eruptions	Acute or subacute cutaneous lupus with epidermal necrosis (Rowell syndrome)

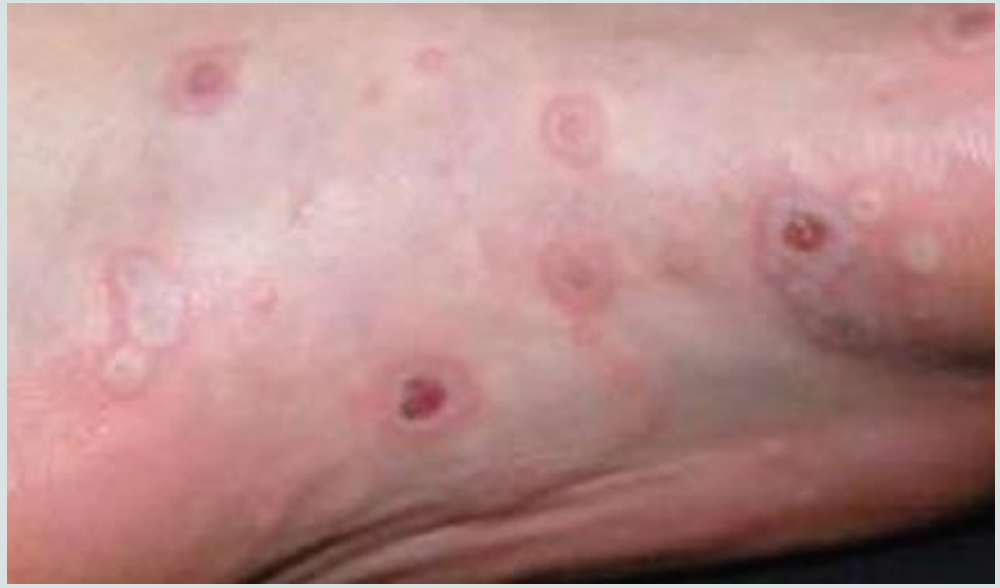
Medicina **2021**, 57, 895

SJS/TNE and EMM (erythema multiform major)

SJS/TEN vs. EM		
	SJS/TEN	EM
Characteristic Lesions	Atypical target lesions: macules with central clearing and 2 poorly demarcated components Large sheets of painful desquamation in later lesions No raised lesion	Typical target lesions: papules with a dark center and 3 well-demarcated, concentric components Raised atypical targets



Med Clin North Am. 2021 Jul;105(4):577-597



Medicina **2021**, 57, 895
JDDG J. Ger. Soc. Dermatol. **2020**, 18, 547–553.

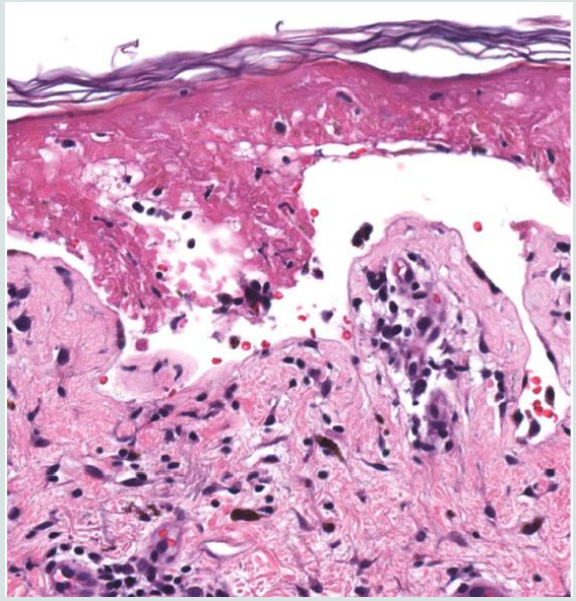
SJS/TNE and EMM (erythema multiform major)

SJS/TEN vs. EM		
	SJS/TEN	EM
Characteristic Lesions	Atypical target lesions: macules with central clearing and 2 poorly demarcated components Large sheets of painful desquamation in later lesions	Typical target lesions: papules with a dark center and 3 well-demarcated, concentric components
Distribution	Typically begins on the face and trunk with centrifugal spread	Face and acral skin, rare involvement of trunk
Triggers	Drugs	Infection (most commonly HSV and *M. pneumonia*)
Mucosal Involvement	Very common—most cases have involvement of ≥2 mucosal surfaces	Rare—typically only one mucosal surface involved if present
Recurrence	Rarely seen with removal and avoidance of causative drug	Frequently seen

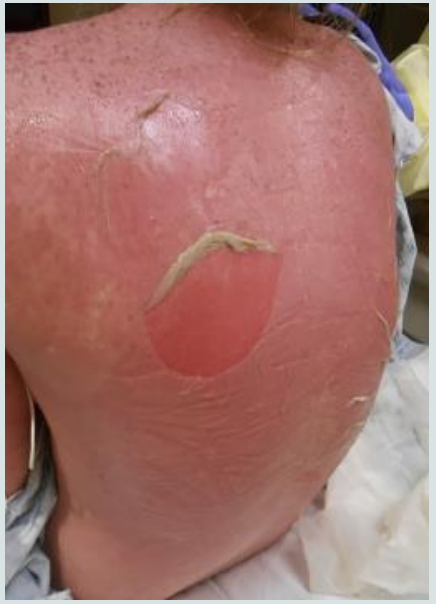
Medicina **2021**, 57, 895

SJS/TEN

- Epidermal detachment at the level of **dermo-epidermal junction**
- Widespread keratinocyte necrosis
- Similar histological finding with erythyma multiform major



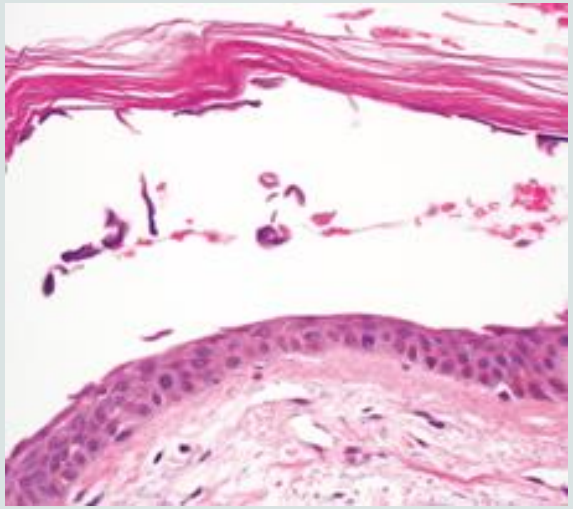
J. Investig. Dermatol. **2016**, 136, 1387–1397.



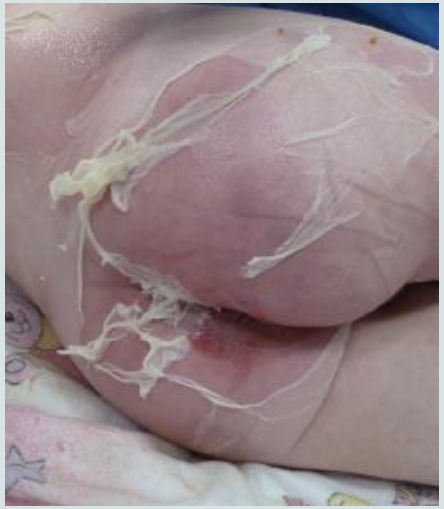
Med Clin North Am. 2021 Jul;105(4):577-597.

Staphylococcal scalded-skin syndrome

- Epidermal detachment at the level of **subcorneal** layer



Arch. Pathol. Lab. Med. **2019**, 143, 919–942.



Pediatr Infect Dis J. 2020 Jan;39(1):30-34.

Diagnostic subclassification in pediatric patients

- Drug-induced epidermal necrolysis (DEN)
  - SJS
  - SJS/TEN
  - TEN

Identify and **hold the drug**
Immunosuppressive therapy

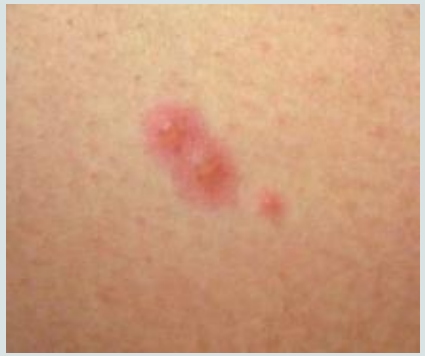
- Reactive infectious mucocutaneous eruption (RIME)
  - Infection related
    - *Mycoplasma pneumoniae*
    - Adenovirus, influenza, et al.
  - Severe mucosal involvement
  - Relatively sparse cutaneous involvement

Identify and **treat infection**
Antimicrobial therapy
Immunosuppressive therapy

F1000Research **2020**, 9, 982

Mycoplasma pneumoniae-induced rash and mucositis (MIRM)

Diagnostic criteris
< 10 % TBSA skin detachment
≧ 2 mucosal sites involved
Few vesiculobullous lesions, or scattered atypical targets
Evidence of atypical pneumonia



Conjunctivitis
Eyelid edema
Hemorrhagic crusting

J. Am. Acad. Dermatol. **2015**, 72, 239–245.e4
Pediatric Dermatol. **2020**, 38, 306–308.

Clinical characteristics of MIRM

Systemic review, 202 patients of MIRM

Age, y	11.9 ± 8.8
Gender	
Male	121 (66)
Female	62 (34)
Unknown	19 (10)
Cutaneous distribution	
Acral	42 (46)
Generalized	29 (31)
Truncal	21 (23)
Cutaneous involvement	
Sparse	61 (47)
Absent	42 (34)
Moderate†	24 (19)
Mucosal involvement	
Oral	168 (94)
Ocular	147 (82)
Urogenital	112 (63)
No mucositis	4 (2)

Young patient group
Male predominant

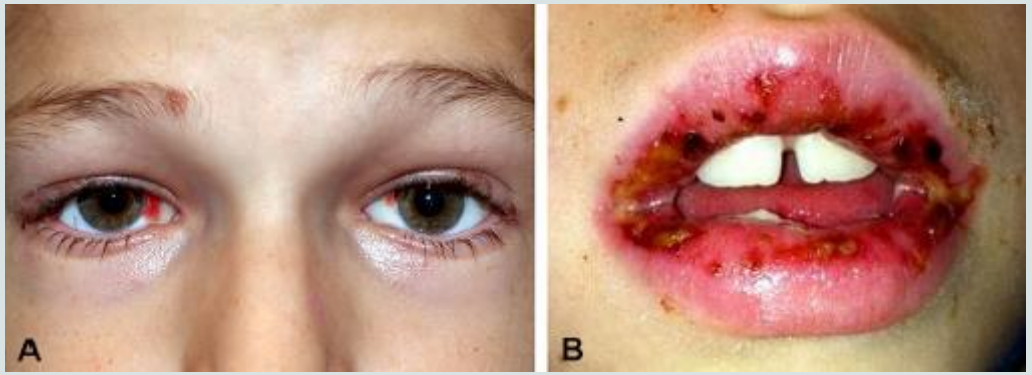
cough, malaise, and fever preceding the eruption by approximately 1 week (mean: 8 ± 6.5 days).

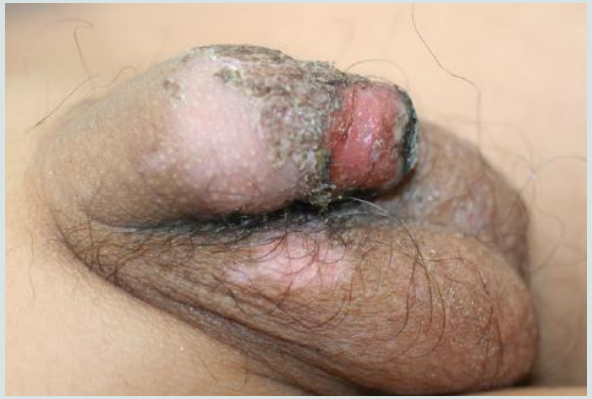
77% patients had sparse or absent cutaneous involvement

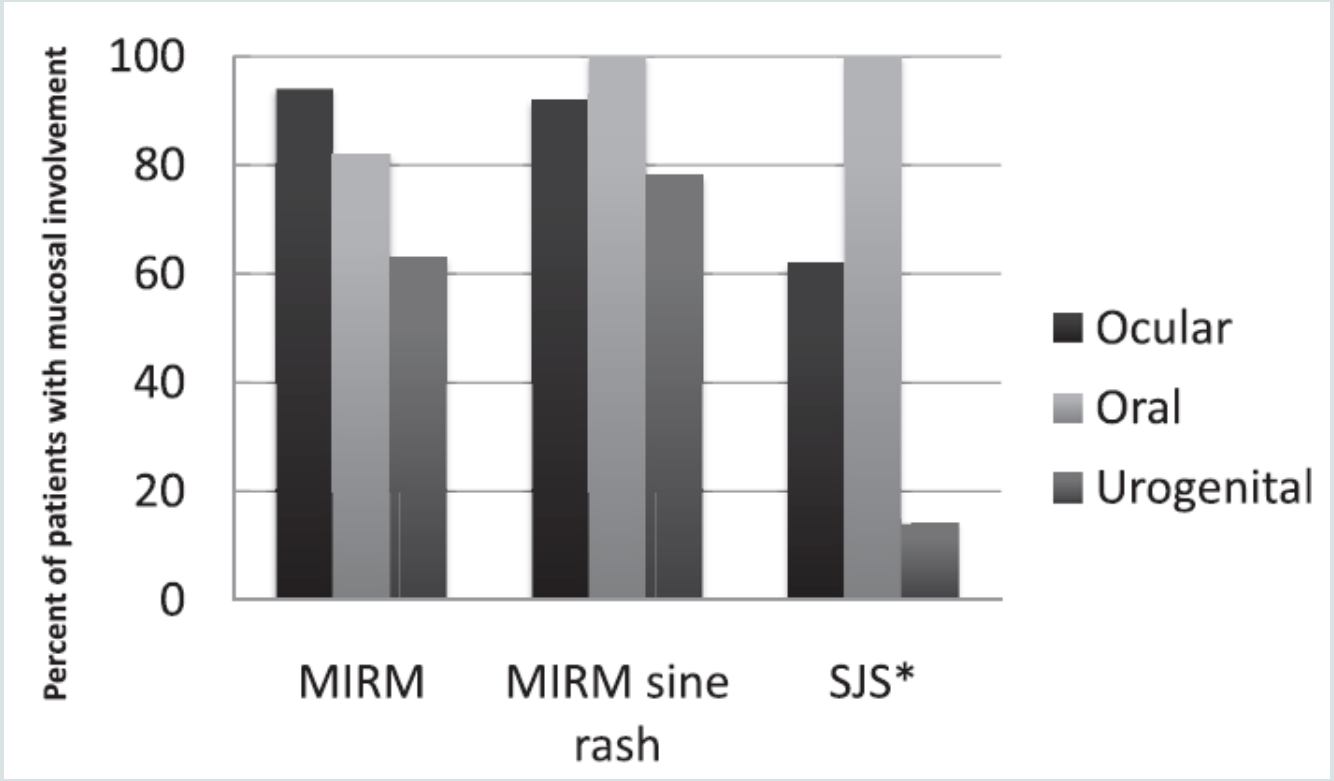
Predominant mucosal involvement
Mortality 3%

J. Am. Acad. Dermatol. **2015**, 72, 239–245.e4

MIRM revealed more ocular and urogenital involvement than SJS







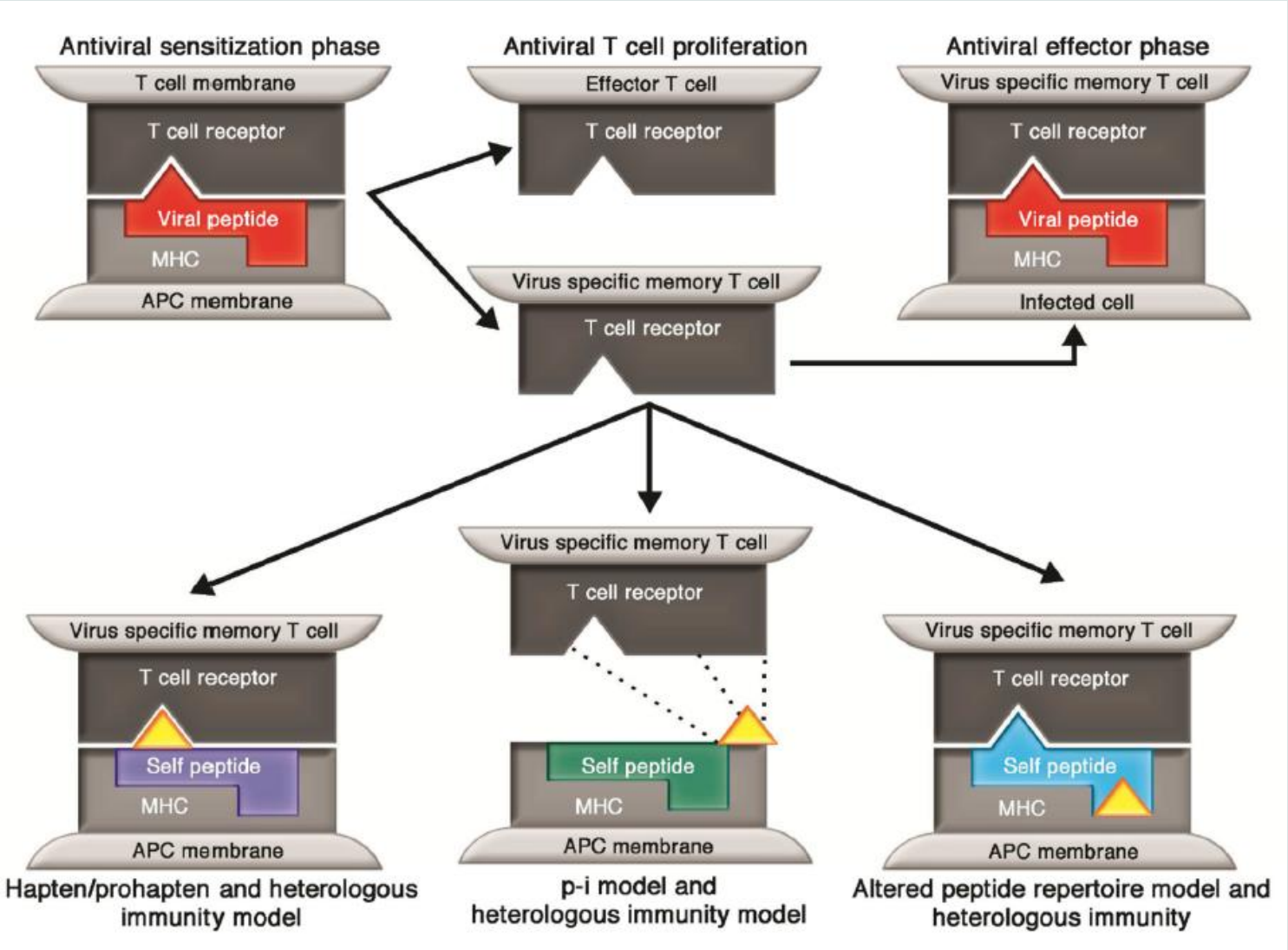
Systemic review, 202 patients of MIRM

J. Am. Acad. Dermatol. **2015**, 72, 239–245.e4

Pathophysiology

- Still not been fully elucidated
- **Cytotoxic T lymphocytes mediated**, type IV hypersensitivity reactions
- Widespread epithelial keratinocyte apoptosis and necrosis
- Several hypotheses
    - Hapten/pro–hapten concept
    - Pharmacological interaction concept
    - Altered peptide concept

The immune response of SJS/TEN



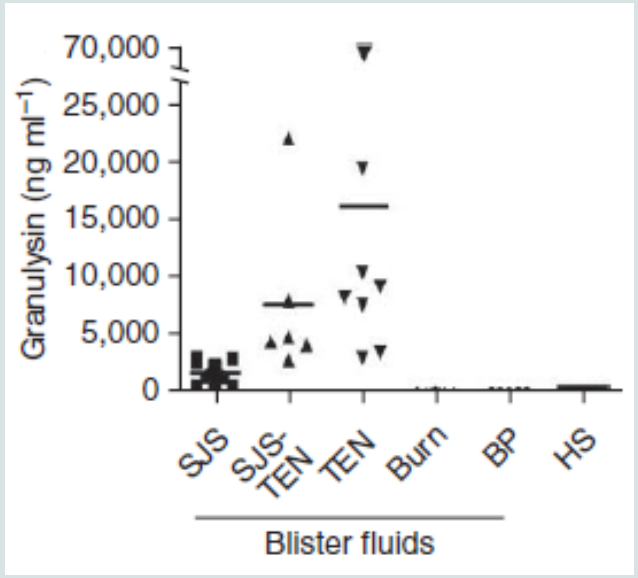
Pharmacological interaction concept

J Allergy Clin Immunol. 2015; 136(2): 219–34

Granulysin is a key mediator for disseminated keratinocyte death

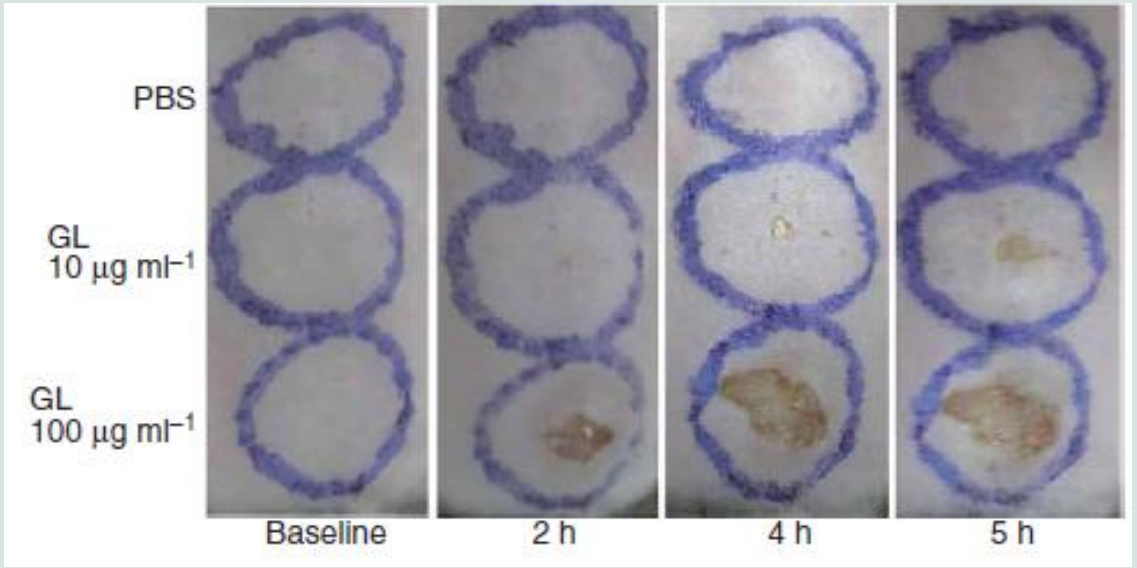
- Granulysin is a cytolytic and proinflammatory molecule expressed by activated human cytotoxic T lymphocytes and natural killer cells

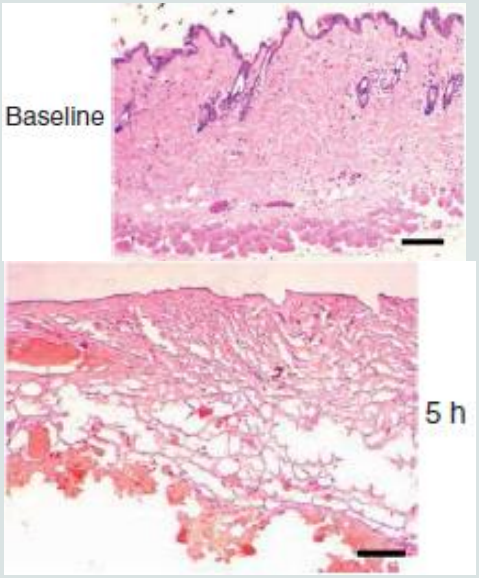
Blister fluid revealed granulysin protein levels were correlated with the severity of the disease



ELISA

Injection of granulysin into the skin of mice induced an SJS/TEN-like reaction



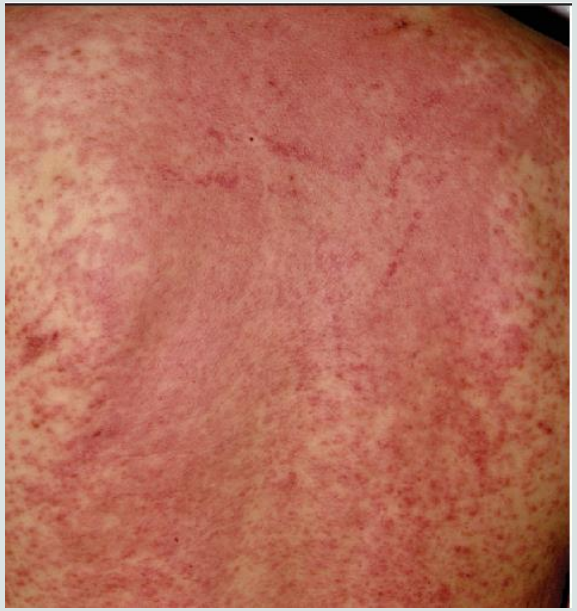


Nat. Med. **2008**, 14, 1343–1350

Granulysin is not specific for SJS/TEN

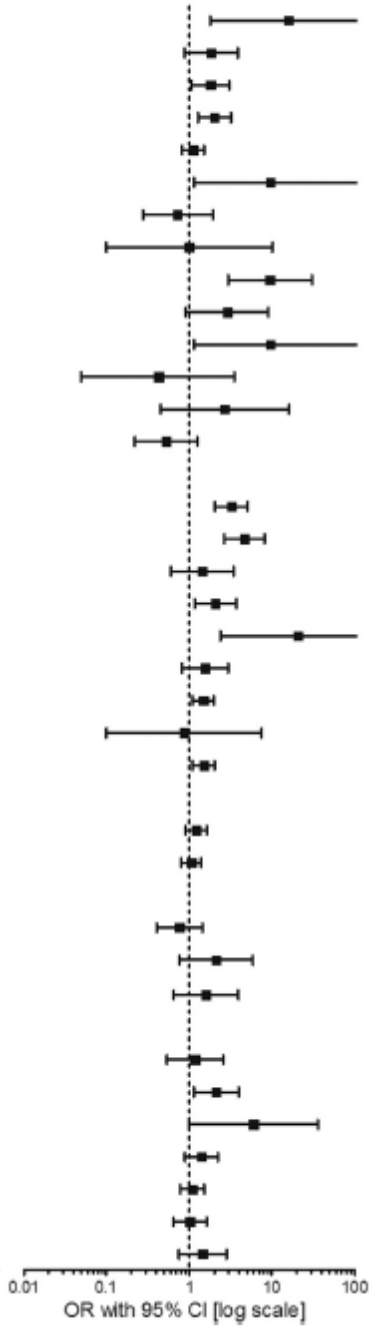
- Consistent across all cytotoxic T-lymphocyte (CTL)-mediated bullous blistering disorders
  - Erythema multiform major
  - Bullous fixed drug eruption
- Patients with drug reaction with eosinophilia and systemic symptoms (DRESS)

Skin expression of DRESS



1. Br. J. Dermatol. **2012**, 167, 452–453.
2. Eur J Dermatol. 2011 May-Jun;21(3):385-91.

	Number of cases (%) (n=480)		Number of controls (%) (n=1920)		Odds ratio
Diseases previously associated with SJS/TEN					
Lupus erythematosus	<5	(<1.0)	<5	(<0.3)	16.00
Other collagen vascular disease	11	(2.3)	25	(1.3)	1.83
Pneumonia diagnosed <120 days prior	<5	(<1.0)	<5	(<0.3)	1.80
Active cancer*	29	(6.0)	61	(3.2)	2.01
Non-active cancer†	79	(16.5)	303	(15.8)	1.12
Bone cancer	<5	(<1.0)	<5	(<0.3)	9.66
Breast cancer	5	(1.0)	27	(1.4)	0.73
Colon cancer	<5	(<1.0)	<5	(<0.3)	1.00
Hematologic cancer	10	(2.1)	5	(0.3)	9.46
Cancer of the nervous system	5	(1.0)	7	(0.4)	2.86
Ovarian cancer	<5	(<1.0)	<5	(<0.3)	9.66
Prostate cancer	<5	(<1.0)	9	(0.5)	0.43
Cancer of the respiratory tract	<5	(<1.0)	<5	(<0.3)	2.67
Skin cancer	7	(1.5)	48	(2.5)	0.53
Diseases usually treated with high risk drug for SJS/TEN					
Epilepsy	35	(7.3)	47	(2.5)	3.22
New use of antiepileptic drug ≤84 days	28	(5.8)	26	(1.4)	4.65
No new use of antiepileptic drug ≤84 days	7	(1.5)	21	(1.1)	1.44
Gout	20	(4.2)	43	(2.2)	2.08
New use of allopurinol ≤84 days	5	(1.0)	<5	(<0.3)	20.48
No new use of allopurinol ≤84 days	15	(3.1)	42	(2.2)	1.55
Depression and other affective disorders	80	(16.7)	240	(12.5)	1.48
New use of SSRI ≤84 days	<5	(<1.0)	5	(0.3)	0.88
No new use of SSRI ≤84 days	79	(6.4)	235	(12.2)	1.49
Allergies					
Hay fever / Allergic rhinoconjunctivitis	77	(16.0)	266	(13.9)	1.21
Asthma	83	(17.3)	318	(16.6)	1.06
Autoimmune diseases					
Psoriasis	12	(2.5)	62	(3.2)	0.77
Polymyalgia rheumatica	6	(1.3)	12	(0.6)	2.11
Rheumatoid arthritis	7	(1.5)	18	(0.9)	1.59
Other common diseases					
COPD	9	(1.9)	31	(1.6)	1.18
Chronic kidney disease	17	(3.5)	35	(1.8)	2.12
Acute kidney disease (<365 days)	<5	(<1.0)	<5	(<0.3)	6.00
Diabetes mellitus type 2	28	(5.8)	83	(4.3)	1.40
Hypertension	77	(16.0)	294	(15.3)	1.09
Hyperlipidemia	29	(6.0)	110	(5.0)	1.02
Myocardial infarction	13	(2.7)	37	(1.9)	1.45



Risk factors of SJS/TEN

- CPRD database (Jan 1995 to Dec 2013)

  (Clinical Practice Research Datalink)
- Lupus erythematosus
- Pneumonia within 120 days
- Chronic kidney disease
- Active cancer (mainly hematologic cancer)
- New use of antiepileptic drug ≦84 hours
- New use of allopurinol drug ≦84 hours
- HIV infection (1-2/1000 individuals)[1]

J Invest Dermatol. 2017 Jun;137(6):1240-1247.
1. Am J Clin Dermatol. 2012 Feb 1;13(1):49-54

Genetic factor-HLA types

HLA-I genotypes and medication associations in Stevens-Johnson syndrome/toxic epidermal necrolysis

Medication	HLA-I Genotype	Population
Sulfamethoxazole	HLA-B*38	European
Sulfamethoxazole-Trimethoprim	HLA-B*15:02-V*0801	Thai
Methazolamide	HLA-B*59:01 HLA-CW*1:02	Korean, Japanese
Lamotrigine	HLA-B*15:02	Han Chinese
Phenytoin	HLA-B*15:02	Han Chinese, Thai
Allopurinol	HLA-B*58:01	Han Chinese, Caucasian, Thai, Japanese
Carbamazepine[a]	HLA-B*15:02 HLA-A*31:01 HLA-B*15:11	Han Chinese (B*15:02)[14,31]
Aromatic antiepileptics (oxcarbazepine, phenytoin, lamotrigine)	HLA-B*15:02	Multiple/nonspecific[33]

60% allopurinol-SJS

100% carbamazepine-SJS

J Allergy Clin Immunol. 2015; 136(2): 219–34
Med Clin North Am. 2021 Jul;105(4):577-597

Drugs are the most common trigger of SJS/TEN

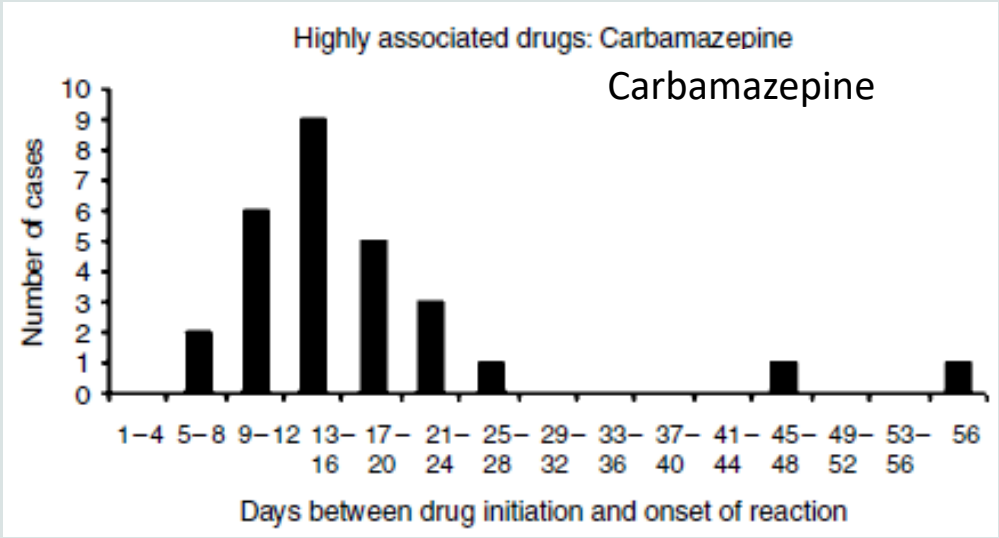
Common Drug Triggers of SJS/TEN	
Anti-epileptics	Antibiotics
○ Lamotrigine	○ TMP-SMX
○ Phenytoin	○ Aminopenicillins
○ Carbamazepine	○ Tetracyclines
○ Valproic Acid	○ Cephalosporins
○ Phenobarbital	Immune Checkpoint Inhibitors
NSAIDs	○ Nivolumab
Allopurinol	○ Pembrolizumab
Nevirapine	

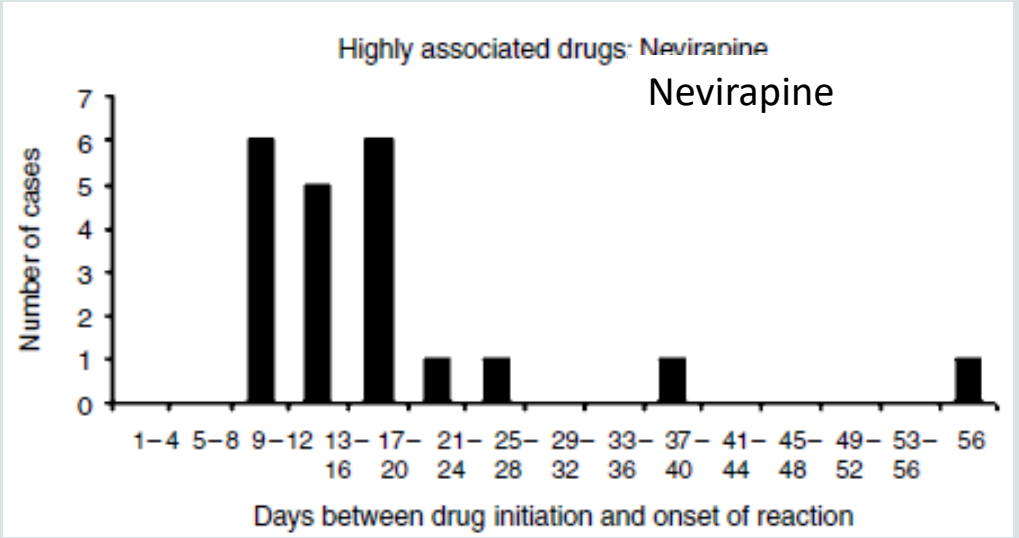
- Paracetamol, aspirin, ibuprofen, and corticosteroid: unclear association,
  - May be confounders used to treat prodromal symptoms.

Medicina **2021**, 57, 895
J. Plast. Reconstr. Aesthetic Surg. 2016, 69, e119–e153

How to identify the causative agent?

- Symptoms typically present **within 8 weeks** of beginning therapy
- Mostly **between 4 days and 4 weeks** of starting a drug
- 15–30% : no offending agent can be identified[1,2]





Multicenter study in Europe: 379 patients

1.Lancet **2017**, 390, 1996–2011.
2.Clin. Pharmacol. Ther. **2010**, 88, 60–68
J Invest Dermatol. 2008 Jan;128(1):35-44.

algorithm of drug causality for epidermal necrosis (ALDEN)

- 列出2個月內的所有用藥
- 用藥及停藥的時間點

Table 5 Details of the algorithm of drug causality for epidermal necrolysis (ALDEN)

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	−3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely −1	>56 Days	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present	
	Excluded −3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b]	

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5 to 28 days

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.

ATC, anatomical therapeutic chemical; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks, tentative list available in complementary table), taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance. [b]Suspected interaction was considered when more than five drugs were present in a patient's body at the same time. [c]Similar drug = same ATC code up to the fourth level (chemical subgroups), see Methods. [d]See definitions for "high risk," "lower risk," and "no evidence of association" in Methods, ref. 15 (detailed list available in complementary table).

Clin. Pharmacol. Ther. **2010**, 88, 60–68

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Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar[c] drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similar[c] drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative −2	Exposure to this drug without any reaction (before or after reaction)	
Dech			
Type			
Othe			
Final score −12 to 10			

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.

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algorithm of drug causality for epidermal necrosis (ALDEN)

- 列出2個月內的所有用藥
- 用藥及停藥的時間點
- 症狀出現時仍在使用此藥物
- 症狀出現時已停藥但時間短於5個半衰期

Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day
	Doubtful −1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present
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	Positive unspecific: 1	Other reaction after use of similar[c] drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative −2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative −2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case–control studies[d]	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case–control studies[d]	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study[d] with sufficient number of exposed controls[c]	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score	−1
		If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	
Final score −12 to 10			

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.

ATC, anatomical therapeutic chemical; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

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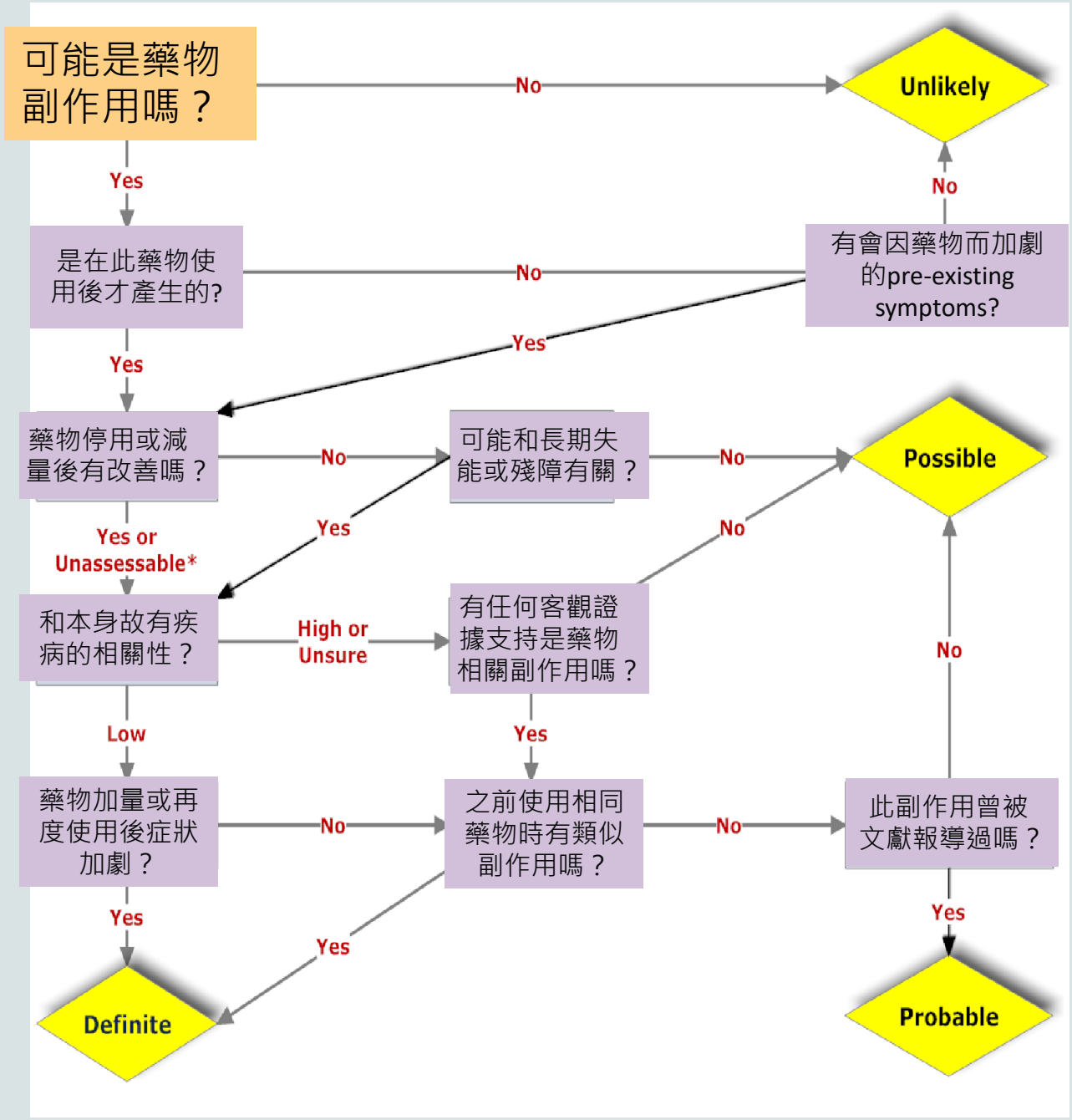
algorithm of drug causality for epidermal necrosis (ALDEN)

- 列出2個月內的所有用藥
- 用藥及停藥的時間點
- 停藥後是否緩解/再次接觸是否惡化
- 此藥物和SJS/TEN的相關性
- 是否可能有其它成因
- Total score: -12 to 10

<0	0–1	2–3	4–5	≧6
Very unlikely	unlikely	possible	probable	Very probable

Clin. Pharmacol. Ther. **2010**, 88, 60–68



PLoS ONE **2011**, 6, e28096.

Lab data

- CBC: Anemia, lymphopenia, neutropenia (Eosinophilia is unusual)
- CRP, **BUN**/Cr, Na/K, Mg, P, **bicarbonate**, **glucose**, liver function, coagulation studies.
- Mycoplasma serology
- CXR
- Skin biopsy
  - From skin lesion, just adjacent to a blister: routine histopathology
  - From peri-blister lesion: for direct immunofluorescence to exclude an immunobullous disorder
- Swabs from skin lesion for bacteriology
  - QOD for three skin lesions (crust or slough area) in acute phase

The severity-of-illness score for Toxic Epidermal Necrolysis (SCORTEN) scale

SCORTEN	
Parameter	**Weight**
Age ≥ 40 years	1
Malignancy—Yes	1
BSA detached > 10%	1
Serum bicarbonate < 20 mmol/L	1
Serum urea nitrogen > 28 mg/dL	1
Serum glucose > 252 mg/dL	1
Tachycardia ≥ 120 bpm	1
Maximum score possible	7

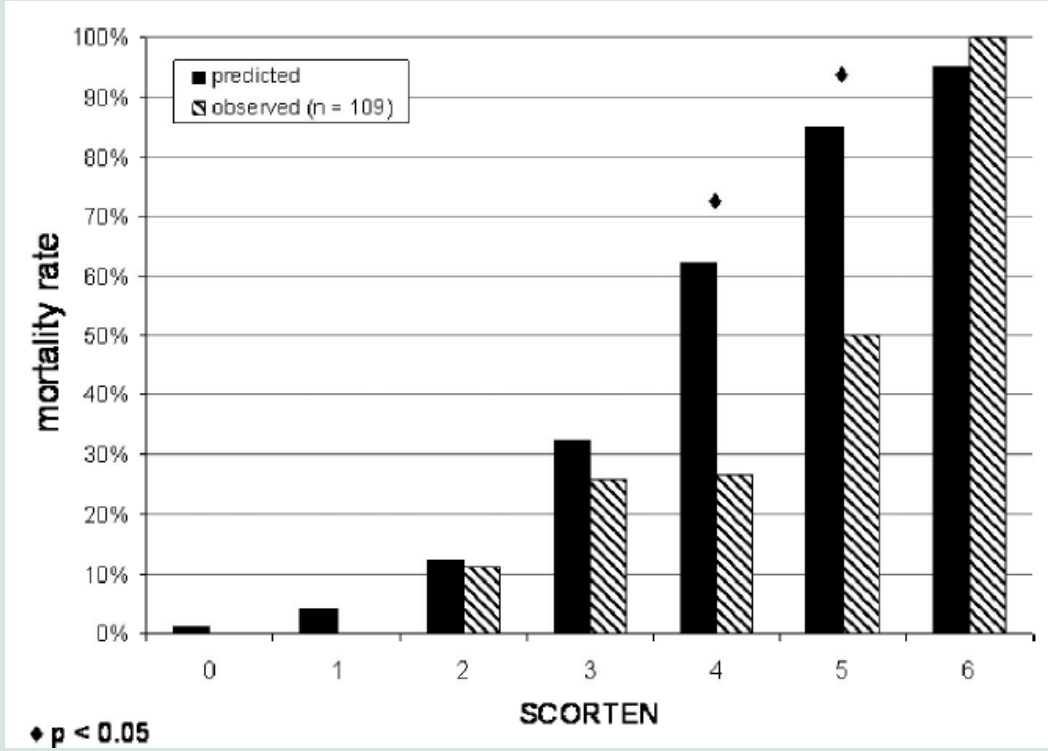
SCORTEN Score	Estimated Mortality (%)
0–1	3.2
2	12.1
3	35.3
4	58.3
>5	>90

- Develop in 2000, predict the mortality of SJS/TEN[1]
- Calculate SCROTEN score at first 24 hr of admission
- BSA involved includes both epidermis that is detachable (positive Nikolsky sign) and epidermis that is already detached

1. J Invest Dermatol. 2000 Aug;115(2):149-53
2. Medicina **2021**, 57, 895

SCROTEN may overestimate the mortality

- Single center
- Retrospective chart review
- 109 patients with TEN
- Overall mortality was 20%
- SCROTEN estimate mortality was 30%
- Overestimate at SCROTEN scale 4 and 5



J. Burn. Care Res. **2006**, 27, 270–275.

ABCD-10 (alternative prognostic algorithm)

ABCD-10	
Parameter	**Weight**
Age ≥ 50 years	1
Serum Bicarbonate < 20 mmol/L	1
Active Cancer—Yes	2
Dialysis prior to adm	3
BSA Involvement > 10%	1
	8

Age ≧ 40 y/o

1

BUN > 28 mg/dL

1

ABCD-10 Score	Estimated Mortality (%)
0	2.3
1	5.4
2	12.3
3	25.5
4	45.7
5	67.4
>6	83.6

~~Serum glucose > 252 mg/dL~~

~~Tachycardia ≧ 128 mg/dL~~

Different from SCROTEN

JAMA Dermatol. **2019**, 155, 448–454.

Non-Pharmacologic Treatment

- Cessation of the causative drug (Most important)
- Epidermal loss > 10% BSA → Burn unit care
- Keep room temperature 25–28 ℃
  - Reduce energy consumption and associated metabolic stresses
- Fluid and electrolyte management
- Infection control
- Wound care

Fluid and electrolyte management

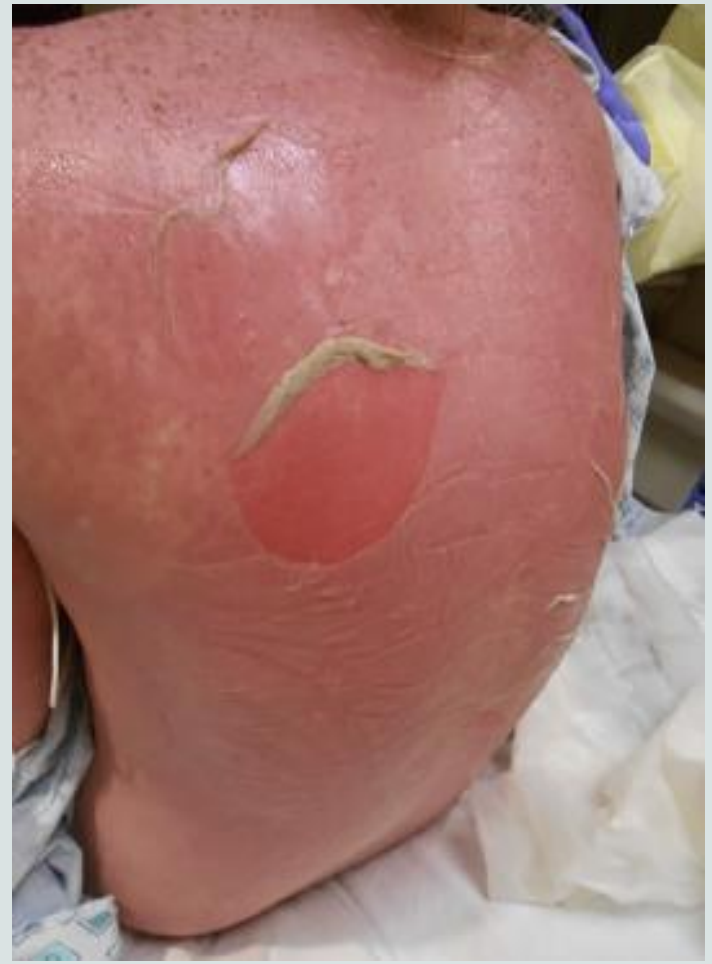
- Insensible losses of fluid, electrolyte and nutrition through wounds
- Enteral feeding as early as possible (NG feeding if oral intake is difficult)
- Urinary catheter when urogenital lesion related dysuria or retention
- Fluid requirement:0.7–2 ml/kg/% affected area when > 15% BSA involved
- Albumin: 5% human albumin, 1 ml/kg/% affected area
- Goal: urine output **0.5–1 mL/kg/h**

Adv. Ther. **2017**, 34, 1235–1244
J Burn Care Res 2010;31:100-4

Wound care

- Minimize shearing forces of skin
- Detached epidermis is left in situ with appropriate dressing
  - Biological dressing to support barrier function
  - Reduce transcutaneous water loss
  - Encourage re-epithelialization
  - Limit microbial colonization
  - Pain control
- If poor healing after conservative treatment

  → surgical debridement



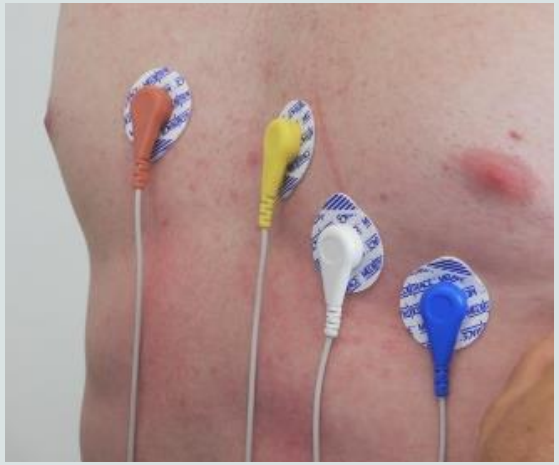
J Plast Reconstr Aesthet Surg 2014;67:1026-32.

Limited skin shearing force on the involved skin of SJS/TEN

Pressure cuff

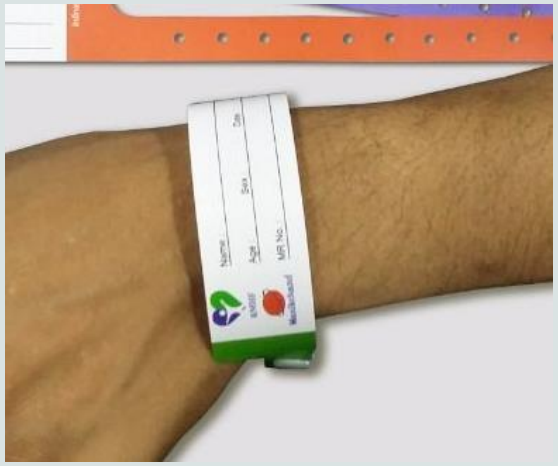
X

Adhesive
EKG leads



X

identification
wrist tags

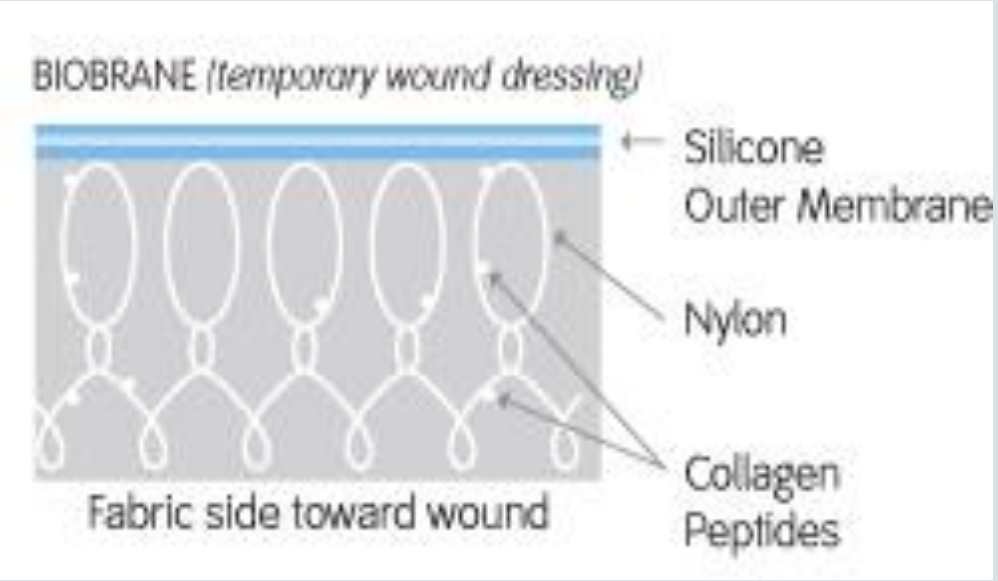


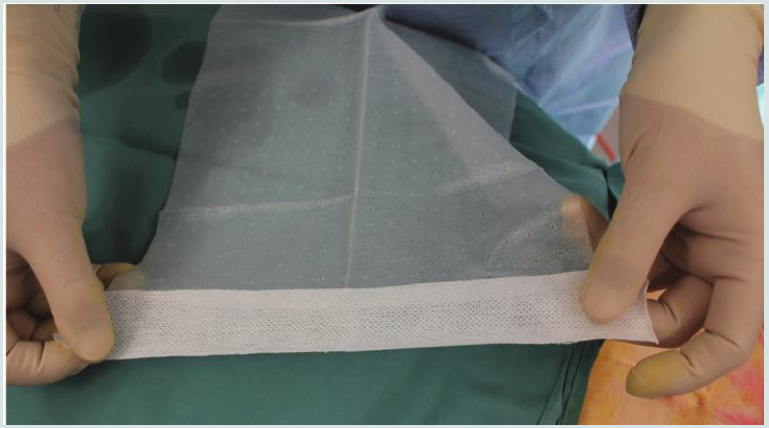
X

Adhesive
dressing

X

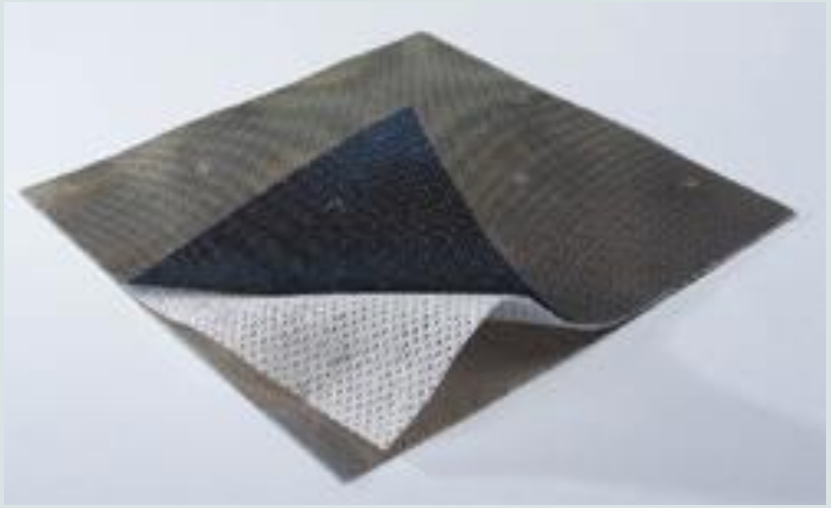
Biobrane



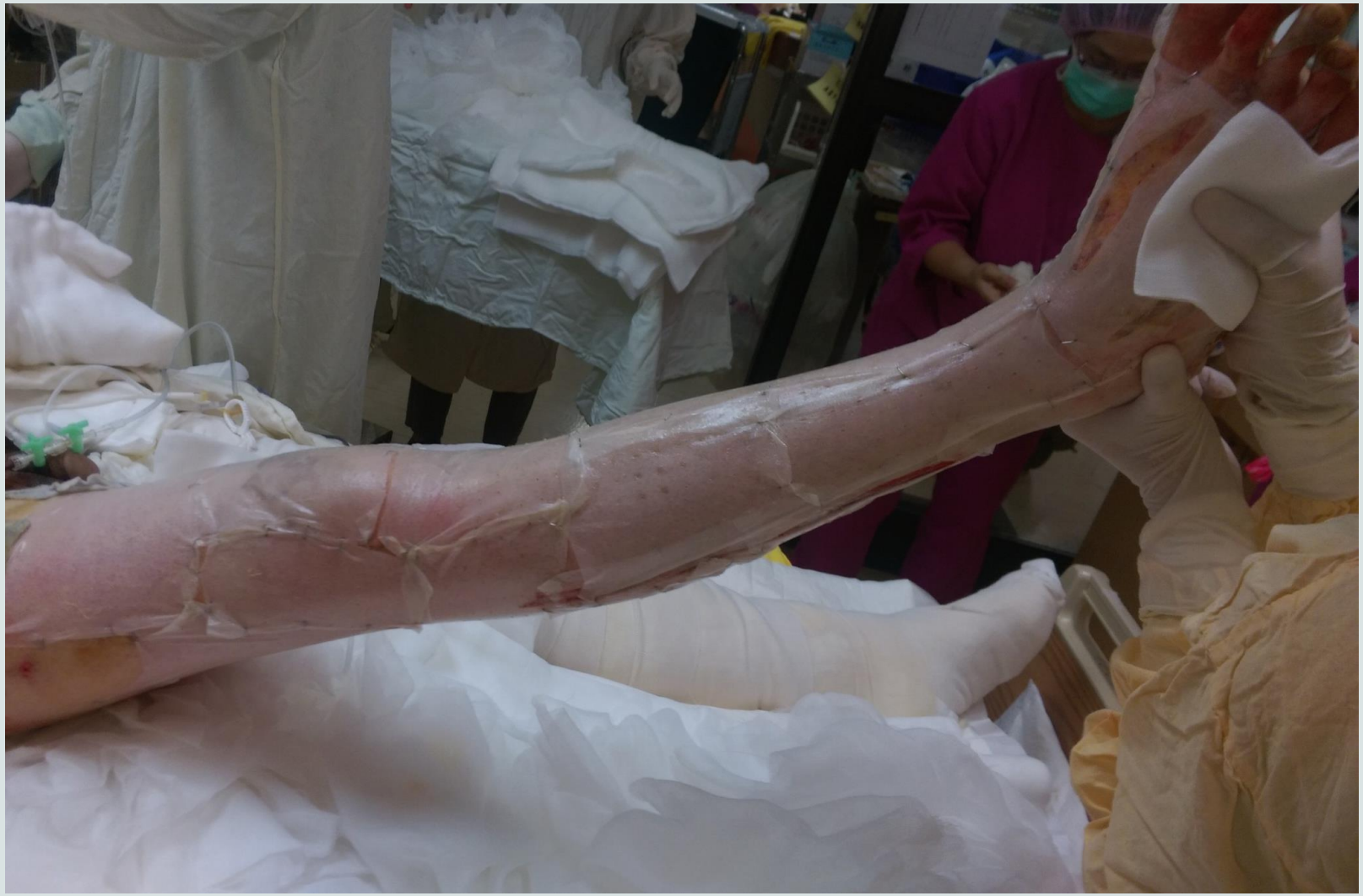


Acticoat

Outer layer: Nanocrystalline silver
Inner layer: absorbent inner core
low adherent polyethylene net



Biobrane



Acticoat

Routine surgical debridement is **controversial**

Retrospective (2000-2015), 40 patients, treatment protocol as below:

- All non-essential medication discontinued
- Supplemental nutrition with Tube feeding
- Fluid replacement (urine output 0.5-1.0 cc/kg/h)
- Do not use steroid
- Debridement of all sloughed skin → Antimicrobial dressing
- IVIG 3-5 day course (1 mg/kg/day)
- Daily monitoring for ocular lesion

Burn **2017**, 43, 200–205.

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- Do not use steroid
- Debridement of all slo
- IVIG 3-5 day course (1
- Daily monitoring for o

SCORTEN	Cases	Predicted mortality (%)	Observed mortality (%)
0	3	3.2	0
1	8	3.2	0
2	11	12.1	9.0
3	7	35.3	28.5
4	3	58.3	33.3
5	1	90.0	0
Unable to determine	7	NA	0
		6.74 (16.7%)	4.0 (10.0%)
Mortality ratio	1.68		

Burn **2017**, 43, 200–205.

Systemic antibiotics only when clinical signs of infection

- Common pathogen
  - initially by *Staphylococcus aureus*
  - Then Gram-negative rods from the digestive flora, ex *Pseudomonas aeruginosa*
- Indiscriminate systemic antibiotics
  - Increase skin colonization, ex *Candida albicans*
- Sign of skin infection
  - Increase in skin pain
  - Increase the depth of wound (ex from superficial dermis to deep dermis)
  - A monoculture of organism is detected from multiple sites
  - Other clinical sign or lab data supports systemic infection or sepsis

J Am Acad Dermatol 1990;23:1039-58

Typical dosing regimens to treat SJS/TEN for selected drugs

- There is no established standard pharmacologic treatment.
- It is difficult to determine if disease remission was due to specific treatment or simply the natural history of the disease.

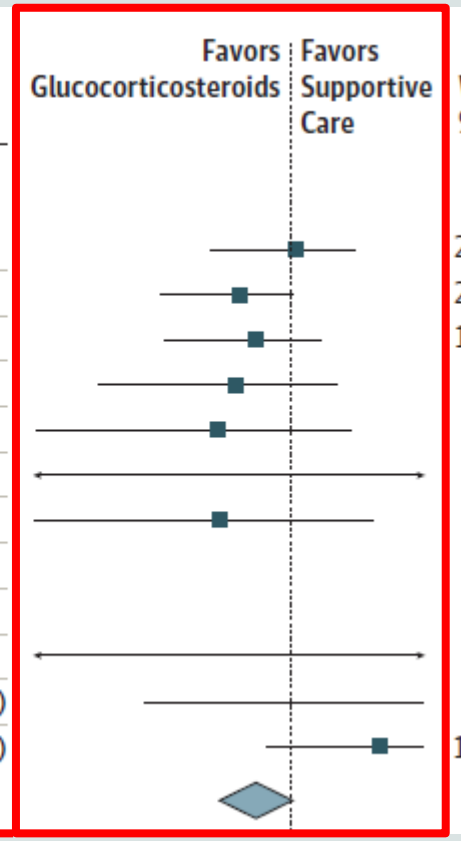
Dosing Regimen for SJS/TEN of Selected Drugs	
IVIg	3 g/kg, divided over 3 days
TNF-alpha inhibitors	- Infliximab: 5 mg/kg as a single dose - Etanercept: Single 50 mg dose
Cyclosporine	2.5–5 mg/kg/day for 7–10 days, followed by gradual taper
Corticosteroids	Prednisone 0.5–1 mg/kg/day or pulse methylprednisolone 1 mg/kg/d for 3 days

Medicina **2021**, 57, 895

The role of corticosteroids as monotherapy is still debated

Meta-analysis for the therapy of SJS and TEN (include 96 studies from 1990–2012)

Study	No. of Patients (Mortality, %) Glucocorticosteroids	Supportive Care	OR (95% CI)	Weight, %
Meta-analysis at the study level Random-effects model				
Dorafshar et al,[18] 2008	20 (25)	11 (36)	0.83 (0.23-3.03)	21.32
Schneck et al,[19] 2008 (DE)	136 (18)	18 (33)	0.30 (0.09-0.99)	24.47
Schneck et al,[19] 2008 (FR)	23 (17)	69 (23)	0.40 (0.10-1.65)	18.14
Barvaliya et al,[20] 2011	25 (12)	6 (33)	0.27 (0.03-2.19)	8.82
Brand et al,[21] 2000	6 (17)	6 (50)	0.20 (0.01-2.88)	5.46
Ioannides et al,[22] 1994	11 (45)	7 (0)	∞ (0.00-∞)	0.00
Kamaliah et al,[23] 1998	20 (5)	5 (20)	0.21 (0.01-4.07)	4.45
Koh et al,[24] 2010	5 (0)	6 (0)	NA	0.00
Léauté-Labrèze et al,[25] 2000	5 (0)	10 (0)	NA	0.00
Sethuraman et al,[26] 2012	10 (30)	9 (0)	∞ (0.00-∞)	0.00
Yip et al,[27] 2005	6 (17)	11 (18)	1.00 (0.07-13.88)	5.62
Azfar et al,[28] 2010	13 (38)	27 (11)	3.66 (0.61-21.97)	11.7
Heterogeneity $I^2 = 5.9\%$ (95% CI, 0%-69.5%), $\tau^2 = 0.05$, $P = .38$			0.54 (0.29-1.01)	



- Glucocorticosteroids
- Supportive care

- Mortality
- OR (95% CI)

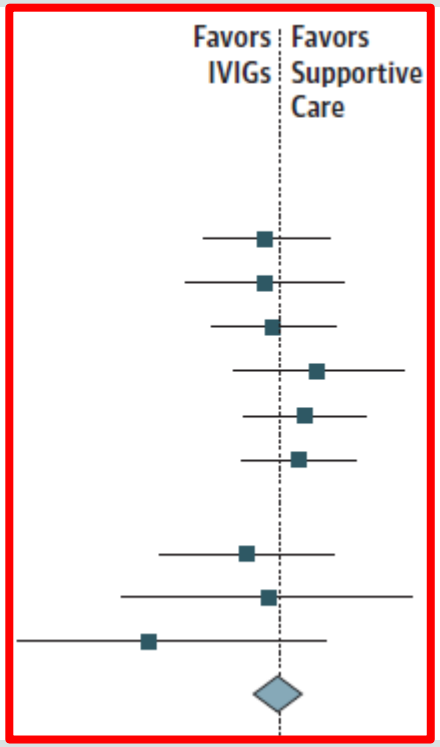
  0.54 (0.29–1.01)

JAMA Dermatol. **2017**, 153, 514–522.

No beneficial finding was observed for intravenous immunoglobulins.

Meta-analysis for the therapy of SJS and TEN (include 96 studies from 1990–2012)

Study	No. of Patients (Mortality, %) IVIG	Supportive Care	OR (95% CI)	Weight, %
Meta-analysis at the study level Random-effects model				
Cartotto et al,[29] 2008	30 (27)	31 (32)	0.76 (0.25-2.31)	15.72
Dorafshar et al,[18] 2008	17 (24)	11 (36)	0.75 (0.19-2.95)	10.23
Firoz et al,[30] 2012	NR	NR	0.88 (0.30-2.56)	16.88
Gravante et al,[31] 2007	17 (41)	15 (27)	1.92 (0.43-8.60)	8.56
Schneck et al,[19] 2008 (DE)	35 (20)	18 (33)	1.50 (0.51-4.45)	16.23
Schneck et al,[19] 2008 (FR)	40 (30)	69 (23)	1.40 (0.51-3.81)	19.16
Atzori et al,[32] 2012	15 (0)	6 (0)	NA	0.00
Shortt et al,[33] 2004	16 (25)	16 (38)	0.56 (0.12-2.53)	8.34
Yip et al,[27] 2005	7 (14)	11 (18)	0.83 (0.06-11.24)	2.83
Paquet et al,[34] 2006	6 (17)	5 (60)	0.10 (0.00-2.15)	2.04
Heterogeneity $I^2 = 0\%$ (95% CI, 0%-42.7%), $\tau^2 = 0$, $P = .77$			0.99 (0.64-1.54)	



- IVIG
- Supportive care

- Mortality
- OR (95% CI)

  0.99 (0.64–1.54)

JAMA Dermatol. **2017**, 153, 514–522.

Corticosteroids and IVIG didn't revealed benefit on mortality

- Systematic population-based follow-up study
- RegiSCAR (International Registry of Severe Cutaneous Adverse Reactions to drugs)
- Jan 2003 – Dec 2007, 442 patients

	Frequency (percentage)	Adjusted[1] HR (95% CI)
Therapies (taking start of therapy into account)		
Supportive therapy only	97 (22%)	1
Corticosteroids	317 (72%)	1.3 (0.8–1.9)
Intravenous immunoglobulins	81 (18%)	1.3 (0.9–2.0)
Any other immunomodulating drug[5]	24 (5%)	0.26 (0.06–1.06)

J. Investig. Dermatol. **2013**, 133, 1197–1204.

No difference of mortality between low and high dose IVIG.

Retrospective, Single center, 28 SJS/TEN and 36 TEN

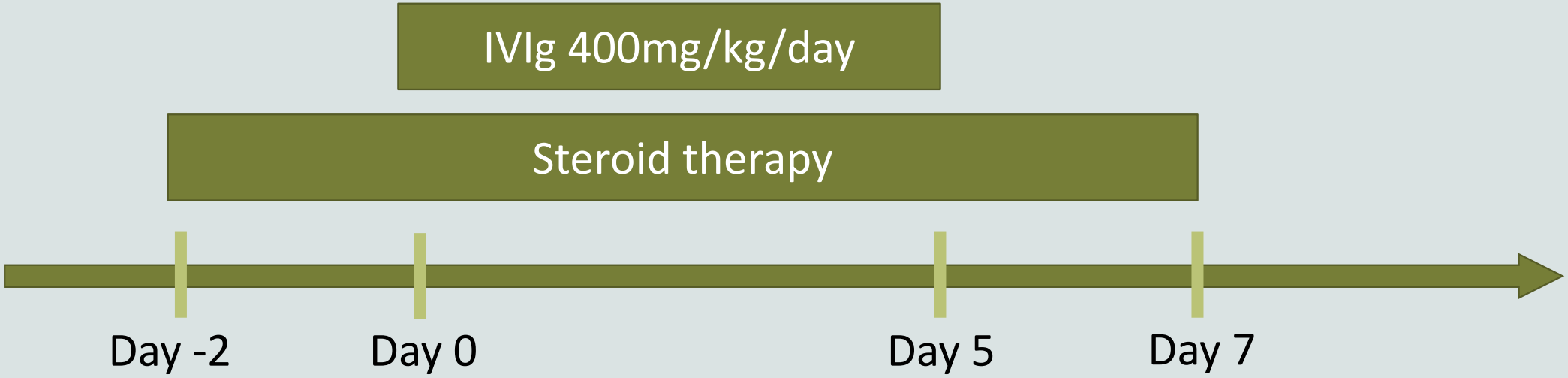
	Mortality	Standardized mortality rate (95% CI)
Patients without prior steroid exposure	12/32 (37.5%)	1.22 (0.52 – 1.90)
Patients with prior steroid exposure	8/32 (25%)	0.95 (0.29 – 1.61)

	Mortality	Standardized mortality rate
Patients with low dose IVIg (< 3g/kg)	13 /42 (31%)	1.08
Patients with high dose IVIg (≧3g/kg)	5/19 (26%)	1.32

Br J Dermatol. 2013 Dec;169(6):1304-9.

Combined steroid with IVIg improve disease severity

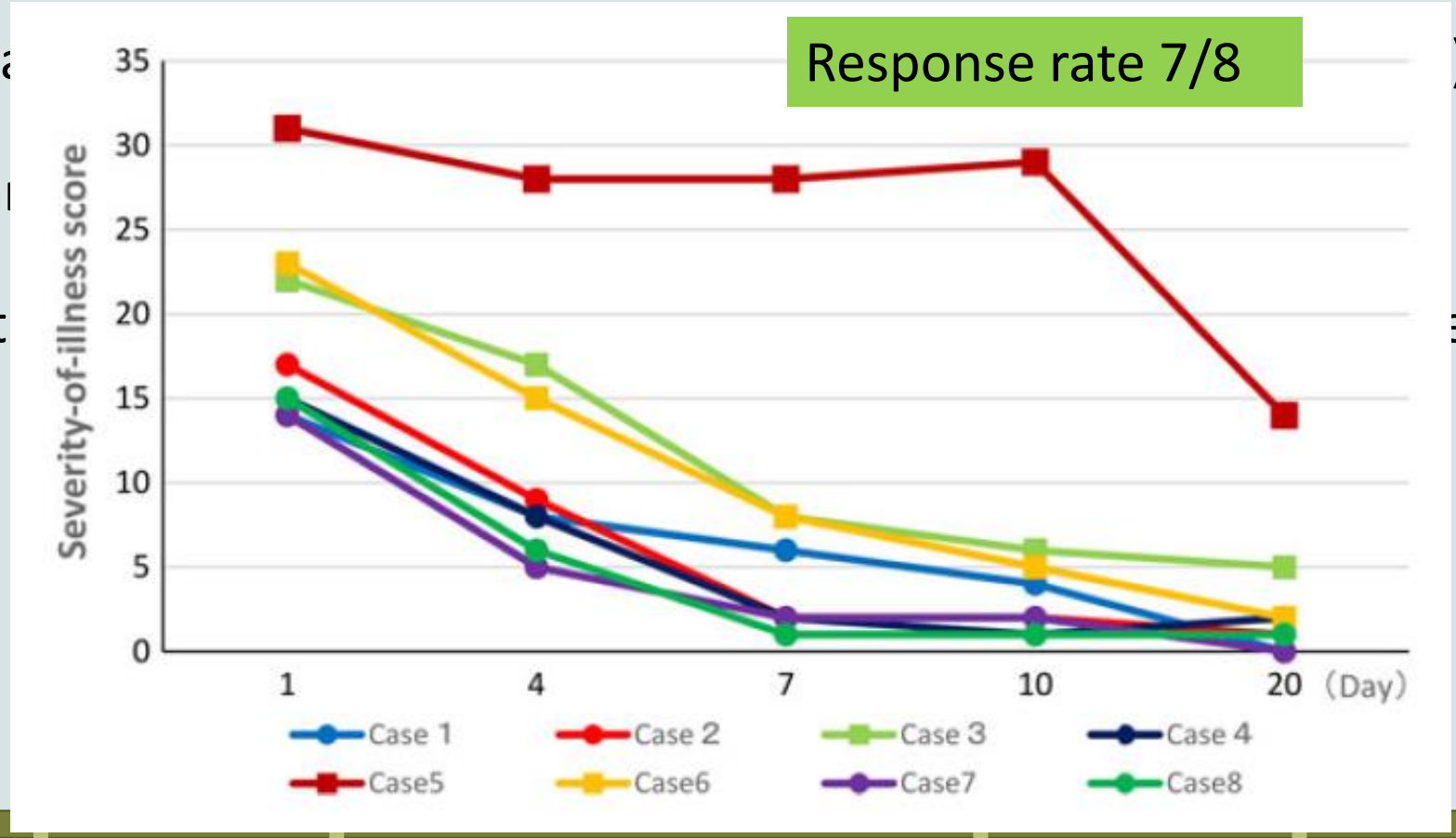
- Open-label, multicenter, single-arm study (Oct 2012 to Apr 2014)
- 8 patients, compare the severity score at day 0 and day 7
- Add IVIg: patients with progressed or unchanged after systemic steroid therapy



J Dermatol. 2015 Aug;42(8):768-77.

Combined steroid with IVIg improve disease severity

- Open-la)
- 8 patie
- Patient erapy



Day -2 Day 0 Day 5 Day 7

J Dermatol. 2015 Aug;42(8):768-77.

Combined steroid with IVIG decreased mortality rate

- Retrospective, multicenter study
- From Jan 2000 to June 2015, 377 patients with SJS/TEN
- Mean IVIG dose: 1.0 g/kg for 3.1 days, total 3.2 g/kg (SD=1.5)
- Mean prednisolone dose: 148.0 mg (SD=182.8) for 9.8 days (SD=15.1)

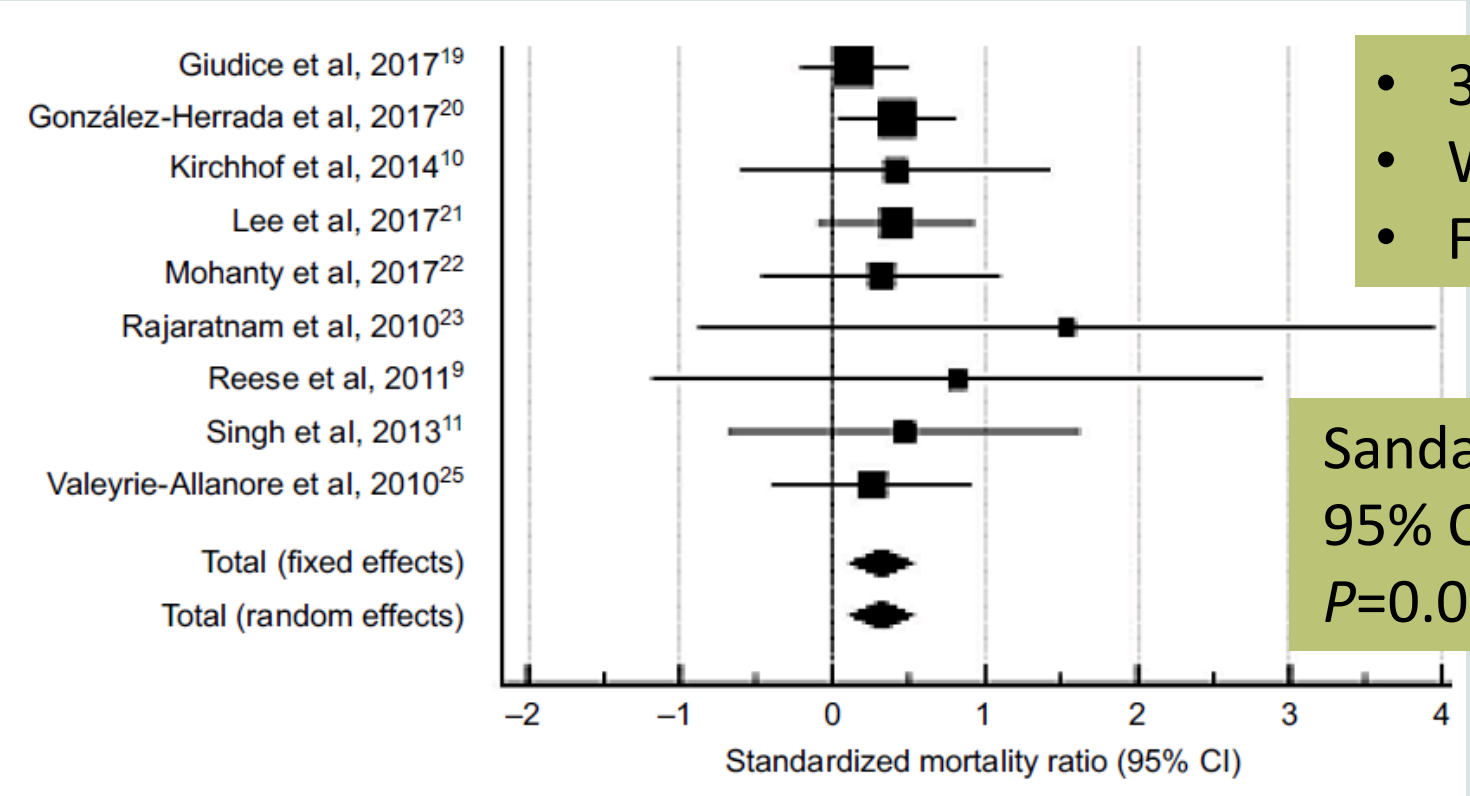
In-Hospital Mortality	Overall N = 368	IVIG Only n = 92	Steroid Only n = 116	IVIG + Steroid n = 54	Supportive Care n = 117
SCORTEN predicted mortality, n (%)	77.7 (21.1)	21.6 (23.5)	20.8 (17.8)	11.6 (20.9)	22.7 (19.4)
Observed mortality, n (%)	54 (14.7)	17 (18.5)	15 (12.9)	6 (10.7)	16 (13.7)
Standardized mortality ratio (95% CI)	0.70 (0.58–0.79)	0.79 (0.55–0.92)	0.72 (0.48–0.89)	0.52 (0.21–0.79)	0.70 (0.47–0.87)

Abbreviations: CI, confidence interval; IVIG, intravenous immunoglobulin; SCORTEN, SCORe of Toxic Epidermal Necrolysis; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

J Invest Dermatol. 2018 Nov;138(11):2315-2321.

Cyclosporin significantly reduced the mortality risk

Meta-analysis, include 12 studies, 358 patients (from January1, 1960 to July 1, 2017)



- 3 –5 mg/kg/day
- Within 24 – 48 hours of onset
- For 5 to 21 days

Sandardized mortality ratio 0.320
95% CI: 0.119–0.522
P=0.002

J. Inflamm. Res. **2018**, 11, 135–142.

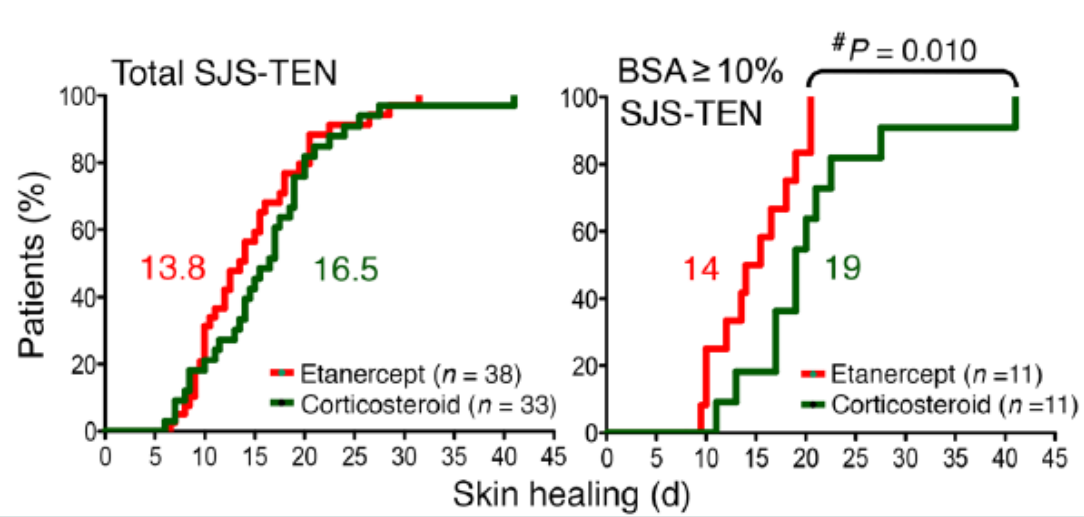
Etanercept decreased the SCROTEN-based predicted mortality rate

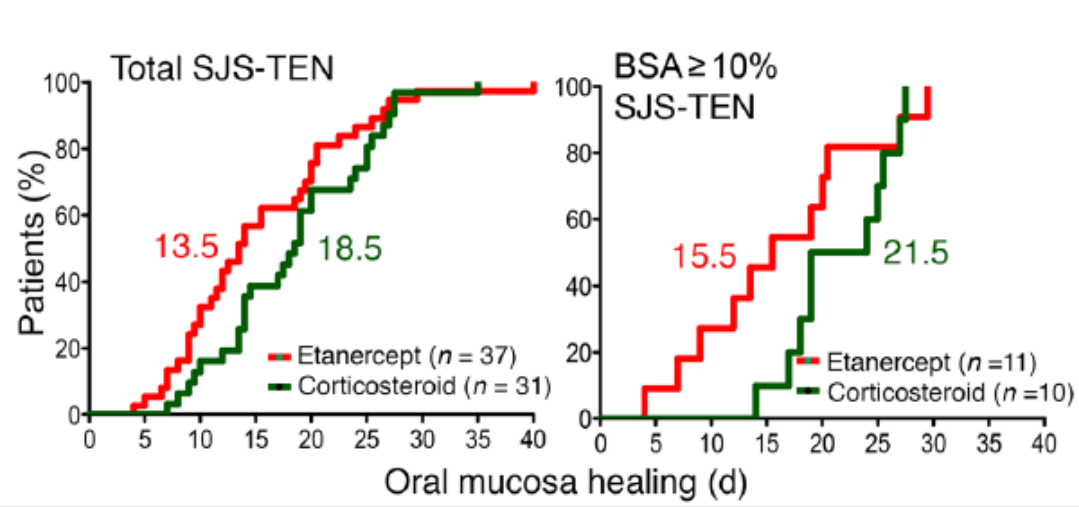
- Randomized, controlled study (2009–2015)
- Etanercept (TNF-α antagonist) (n=48), Corticosteroid (n=43)
- Treatment regimen
  - Etanercept: 25 mg (or 50 mg) subcutaneous injection twice a week
  - Prednisolone: IV, 1–1.5 mg/kg/day
  - until their skin lesions were healed.

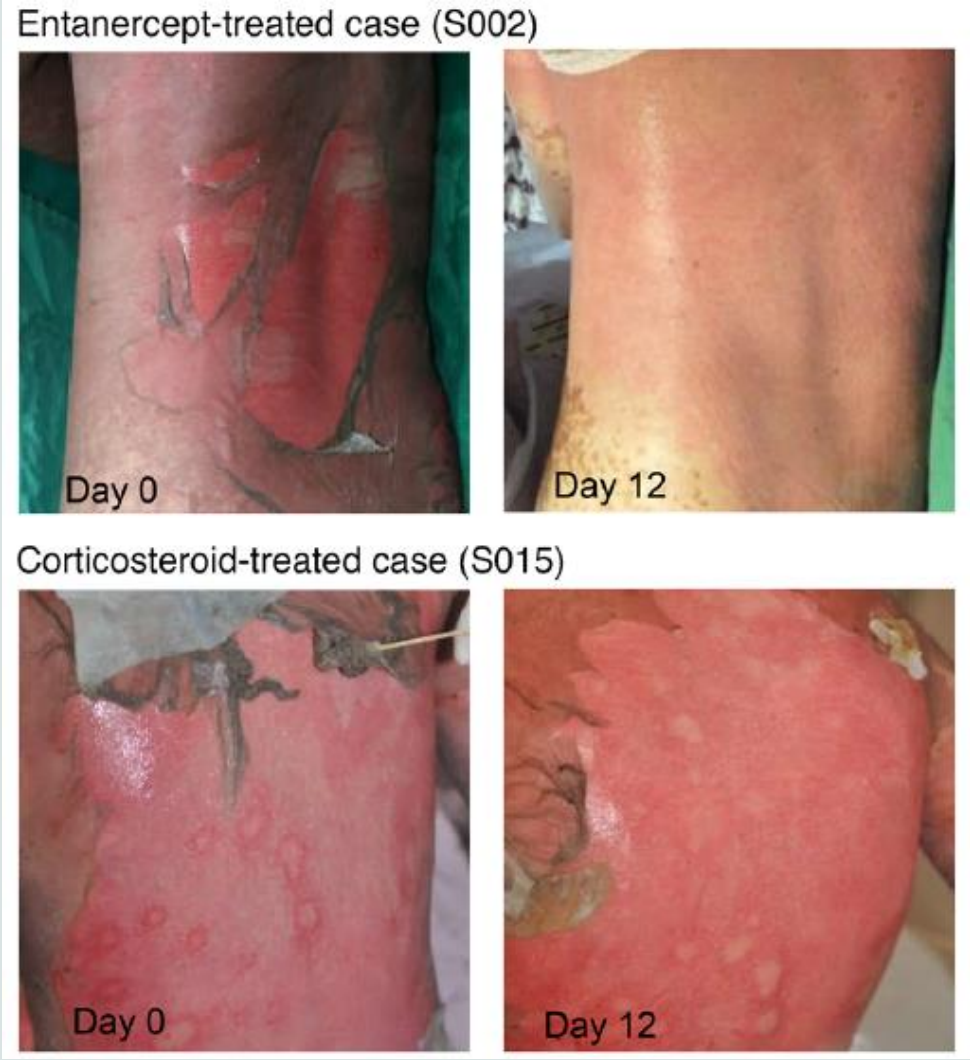
	Etanercept	Corticosteroid	*P* value
SCORTEN, mean ± SD	1.85 ± 1.29	1.95 ± 1.36	0.722
Predicted mortality, %, mean ± SD	17.7 ± 20.5	20.3 ± 25.	0.722
Mortality, patients, %	4/48 (8.3%)	7/43 (16.3%)	0.266

J Clin Invest. 2018 Mar 1;128(3):985-996

Etanercept reduced skin-healing time when comparing to corticosteroid







J. Clin. Investig. **2018**, 128, 985–996.

The pharmacologic treatment of SJS/TEN

- There is no established standard pharmacologic treatment.
- Corticosteroid is not recommended for patients with extensive skin detachment
- The most effective treatment:
  - Cyclosporine
  - a combination of corticosteroids with IVIg

Dosing Regimen for SJS/TEN of Selected Drugs	
IVIg	3 g/kg, divided over 3 days
TNF-alpha inhibitors	- Infliximab: 5 mg/kg as a single dose - Etanercept: Single 50 mg dose
Cyclosporine	2.5–5 mg/kg/day for 7–10 days, followed by gradual taper
Corticosteroids	Prednisone 0.5–1 mg/kg/day or pulse methylprednisolone 1 mg/kg/d for 3 days

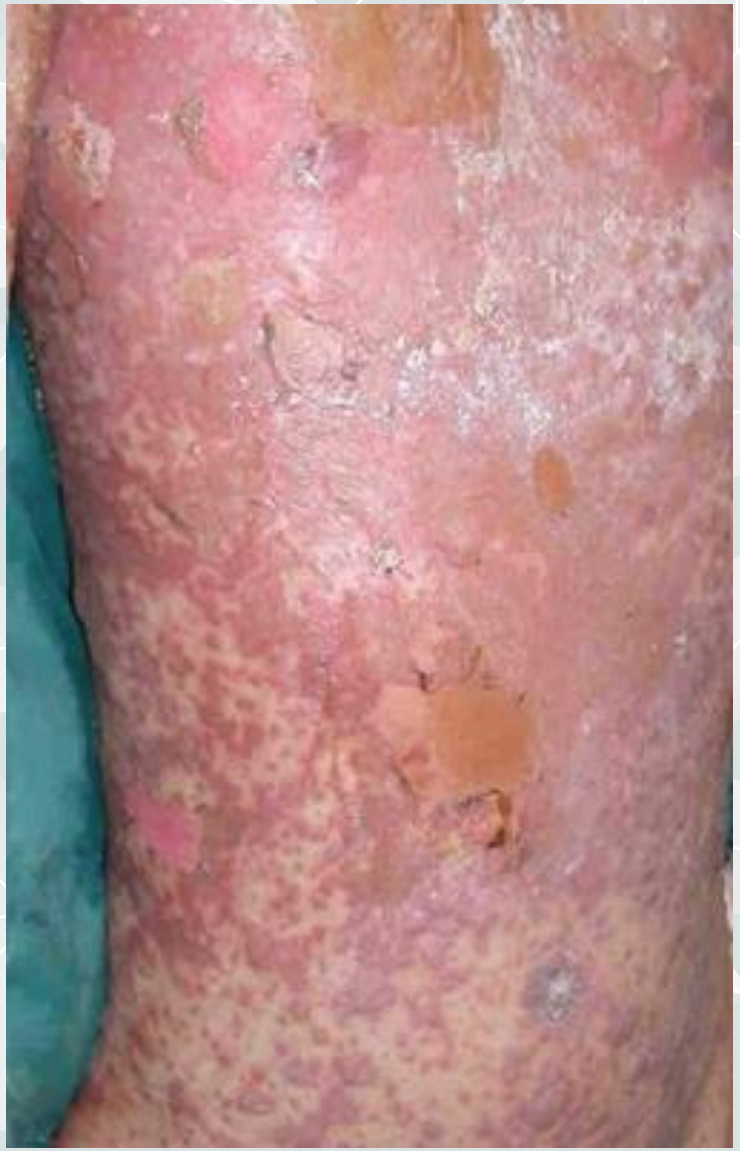
Thalidomide is contraindicated

Medicina **2021**, 57, 895

Take home message

- Differential diagnosis: infection, other vesiculobullous dermatoses
- Identification and cessation of the causative agents
    - The high-risk drug: 5 to 28 days before the onset
    - The moderate-risk drug: 29 to 56 days before the onset
- Evaluate the severity of illness score within 24 hrs after admission and regular re-check
- Supportive care (limit skin shearing force, wound care, prevent infection)
- Cyclosporin and steroid with IVIG may have benefit to mortality

Thanks for your attention!



Mei-Chun Chen, M.D.,Ph. D

Department of plastic and reconstructive surgery

Taipei Veterans General Hospital