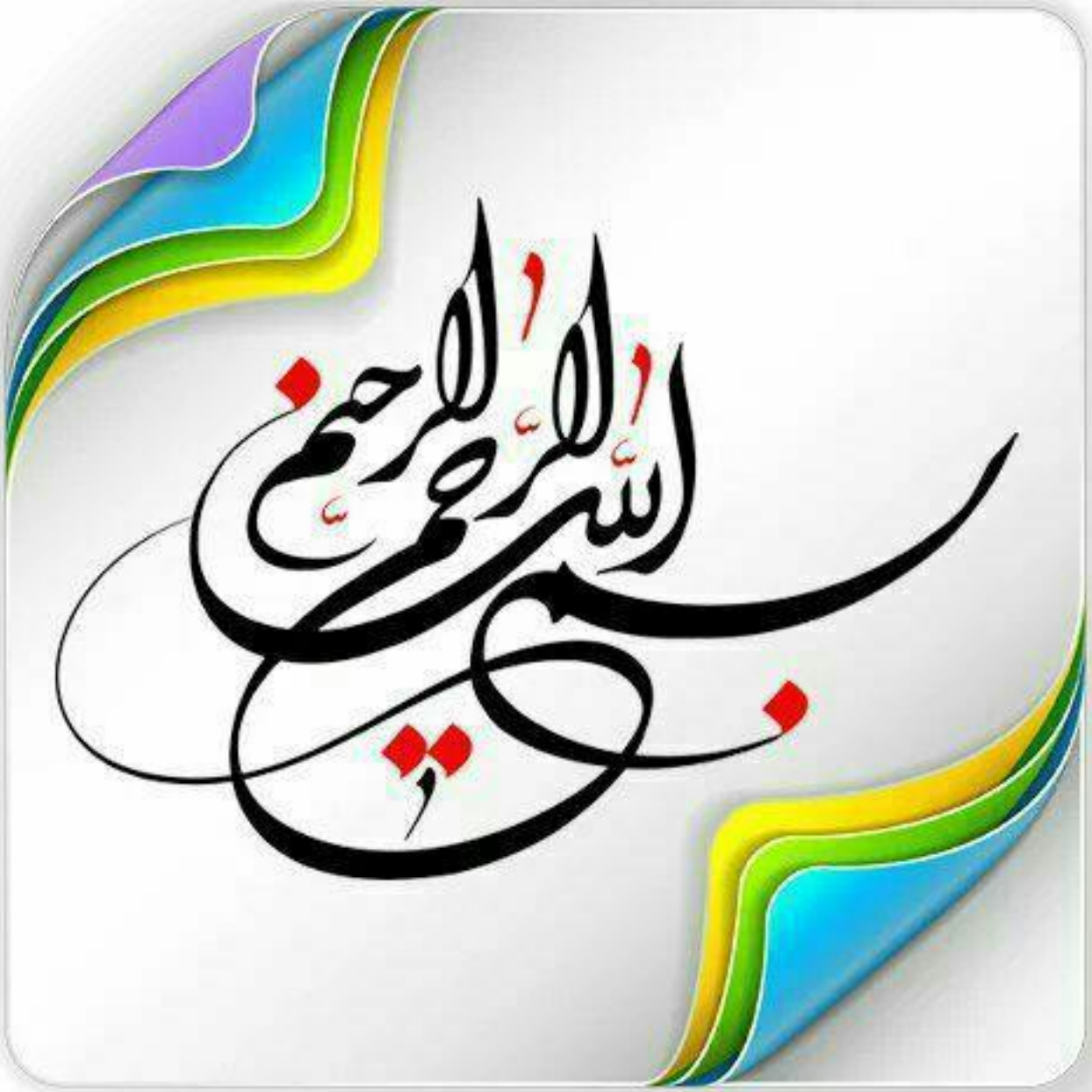
بسم الله الرحمن الرحيم

Toxic Epidermal Necrolysis

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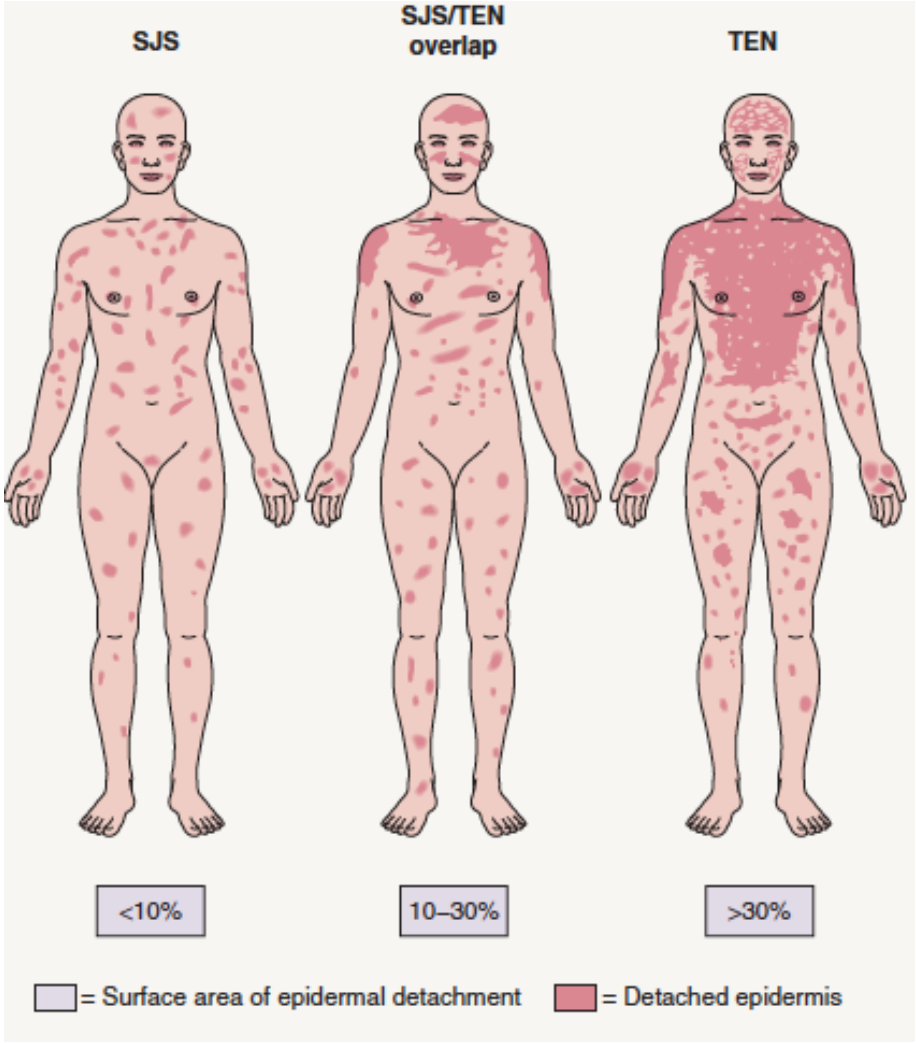
Razi Hospital

Epidermal necrolysis

- SJS and TEN are severe mucocutaneous reactions, most commonly triggered by medications, characterized by extensive necrosis and detachment of the epidermis
- Mucous membranes are affected in over 90 percent of patients, usually at two or more distinct sites (ocular, oral, and genital)

Epidermal necrolysis

- SJS: skin detachment <10%
- TEN: skin detachment >30%
- SJS/TEN:10-30%



Epidemiology

- F/M=1.5 /1
- The overall mortality rate in SJS/TEN: 30% ,10% for SJS, 50% for TEN

Etiologies

- Drugs: strong association in 80% of TEN & 50% of SJS cases
- 4d-4w, limited to first 8 weeks
  - Sulfonamide antibiotics
  - Allopurinol
  - Amine antiepileptics
    - Phenytoin
    - Carbamazepine
  - Lamotrigine
  - NSAIDs

NSAIDs

- Oxicam derivatives: highest risk
- Acetic acid der. such as diclofenac moderate
- Propionic acid derivatives such as ibuprofen no increased risk

Other etiologies

- Vaccinations
- Systemic diseases
- Contrast medium
- External chemical exposure
- Herbal medicines
- Foods
- Bone marrow transplantation
- Radiotherapy plus antiepileptic drugs, localized to areas of radiotherapy

Predisposing factors

- HIV infection: (100-fold higher risk)
- Malignancies especially hematologic(30-60 fold higher risk)
- autoimmune disease such as SLE (50-fold higher risk)
- Concomitant administration of radiotherapy and anticonvulsants (most commonly, those with brain tumors)
- Genetic factors

Genetics

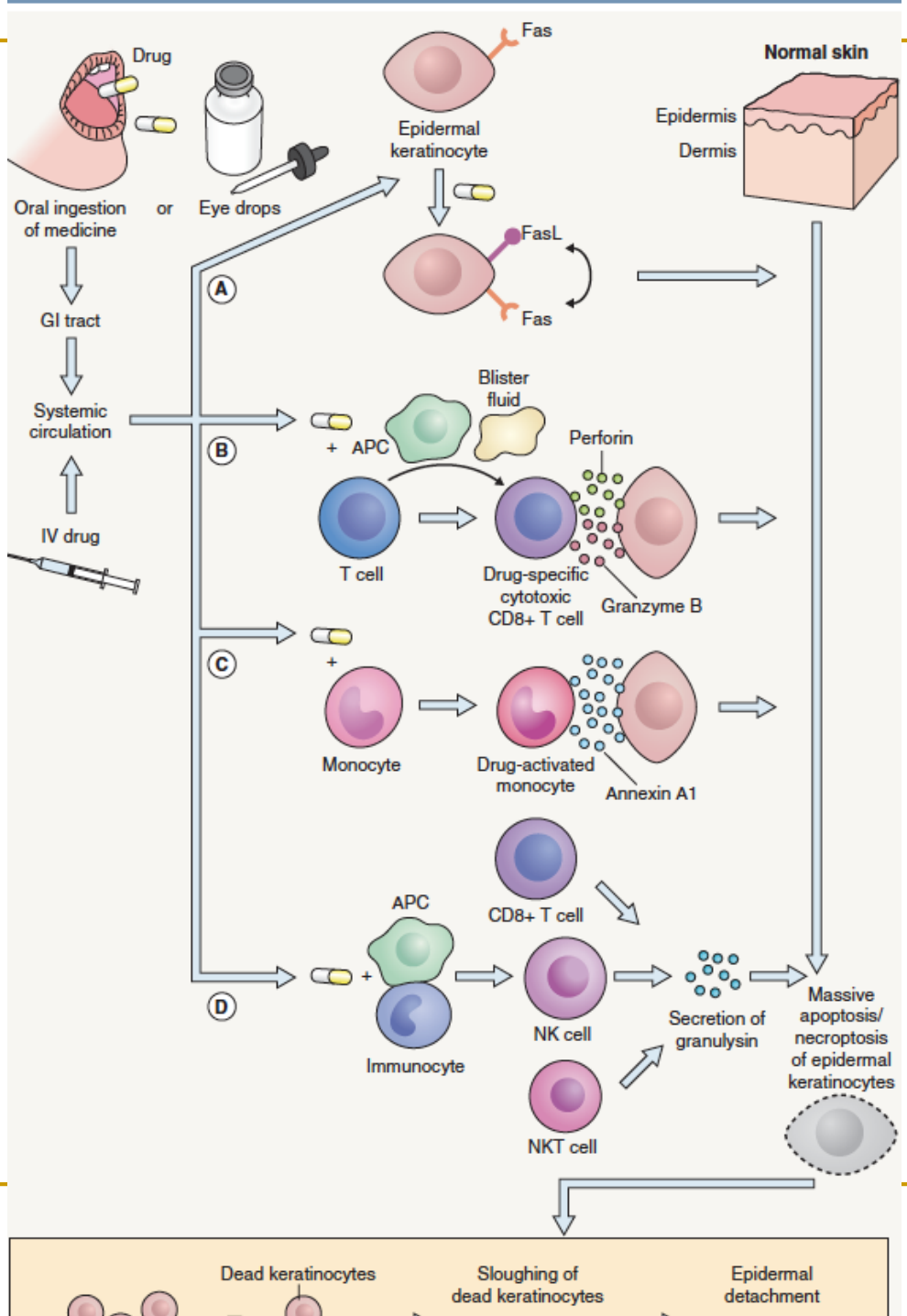
- LA-B*15:02 – Asians (in particular Han Chinese, Thai, Malaysian populations)† and East Indians exposed to carbamazepine
- HLA-B*15:02 – Han Chinese/lamotrigine
- HLA-B*15:02 – Han Chinese/phenytoin
- HLA-A*31:01– Europeans/carbamazepine
- HLA-B*58:01– Han Chinese/allopurinol

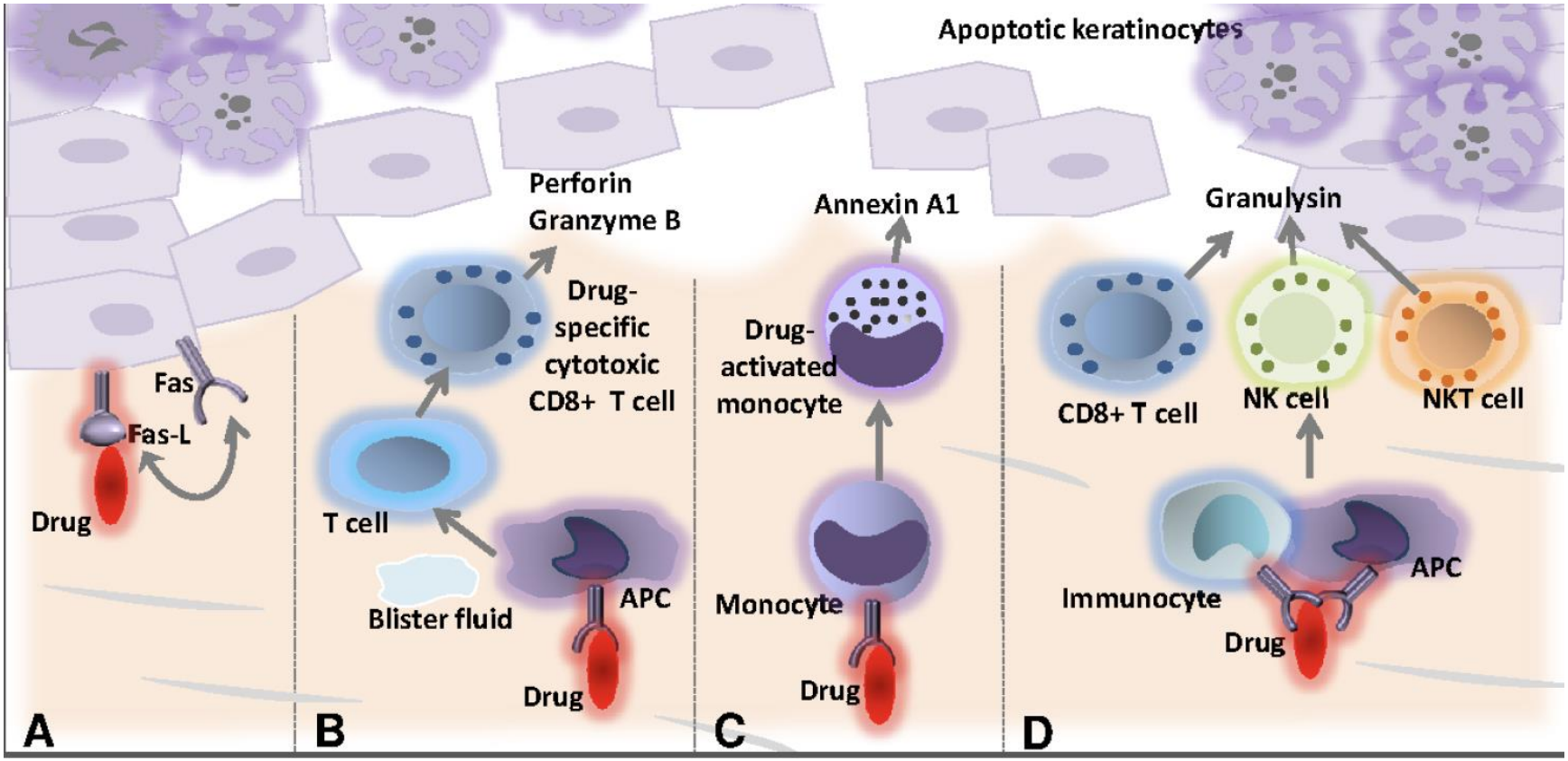
Genetic screening

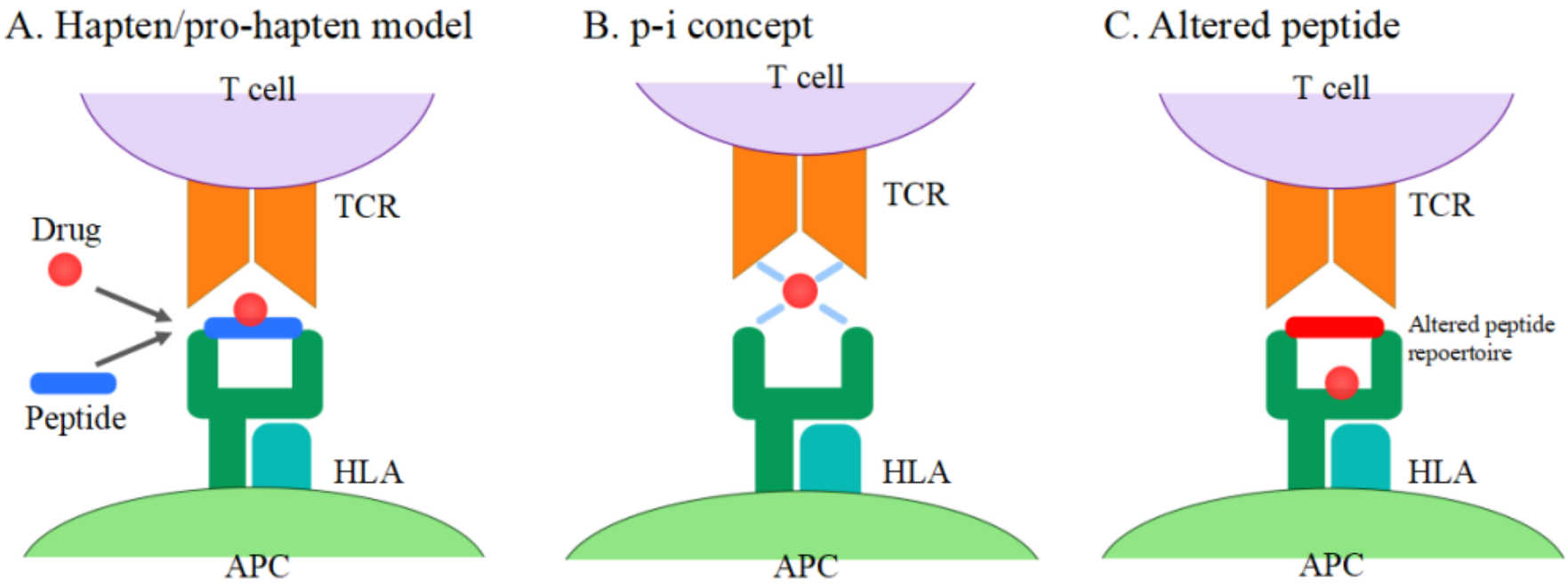
- FDA: screening of Asians for HLA-B*15:02 if use carbamazepine
- One consensus panel has recommended screening all carbamazepine-naïve patients for the HLA-A*31:01
- Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that allopurinol should not be prescribed to carriers of HLA-B*58:01

PATHOGENESIS

- CD8 & NK cells are the major inducers of keratinocyte apoptosis, both directly and indirectly via release of cytotoxic mediators, including Fas ligand, perforin / granzyme, tumor necrosis factor, and granulysin.
- Levels of granulysin in blister fluid correlate with disease severity
- IL-15
- cell-mediated cytotoxic reaction against keratinocytes directed against the native form of the drug rather than a reactive metabolite


Drug
Oral ingestion of medicine
or
Eye drops
GI tract
Systemic circulation
IV drug
Fas
Epidermal keratinocyte
FasL
Fas
Normal skin
Epidermis
Dermis
A
B
C
D
+ APC
Blister fluid
Perforin
T cell
Drug-specific cytotoxic CD8+ T cell
Granzyme B
+
Monocyte
Drug-activated monocyte
Annexin A1
APC
CD8+ T cell
+
Immunocyte
NK cell
NKT cell
Secretion of granulysin
Massive apoptosis/ necroptosis of epidermal keratinocytes
Dead keratinocytes
Sloughing of dead keratinocytes
Epidermal detachment


Apoptotic keratinocytes
Perforin
Granzyme B
Annexin A1
Granulysin
Drug-
specific
cytotoxic
CD8+ T cell
Drug-
activated
monocyte
Fas
Fas-L
Drug
T cell
Blister fluid
APC
Drug
Monocyte
Drug
CD8+ T cell
NK cell
NKT cell
Immunocyte
APC
Drug
A
B
C
D


A. Hapten/pro-hapten model
T cell
TCR
Drug
Peptide
HLA
APC
B. p-i concept
T cell
TCR
HLA
APC
C. Altered peptide
T cell
TCR
Altered peptide
repoertoire
HLA
APC

Clinical manifestation

- Prodrome: Fever, often exceeding 39°C, and flue-like symptoms 1-3d before mucocutaneous lesions
- Photophobia and conjunctival itching or burning, and pain on swallowing may be early symptoms of mucosal involvement
- In some patients, an exanthematous eruption can be the heralding sign of SJS/TEN
- The skin lesions typically begin with ill-defined, coalescing erythematous macules with purpuric centers, although many cases of SJS/TEN may present with diffuse erythema
- The skin is often **tender**

Clinical manifestation

- Start on the face and thorax ,symmetric
- The distal portions of the arms as well as the legs are relatively spared, but the palms and soles can be an early site of involvement.
- The scalp is typically spared
- Atypical target lesions with darker centers may be present
- As the disease progresses, vesicles and bullae form and within days the skin begins to slough

Nikolsky sign

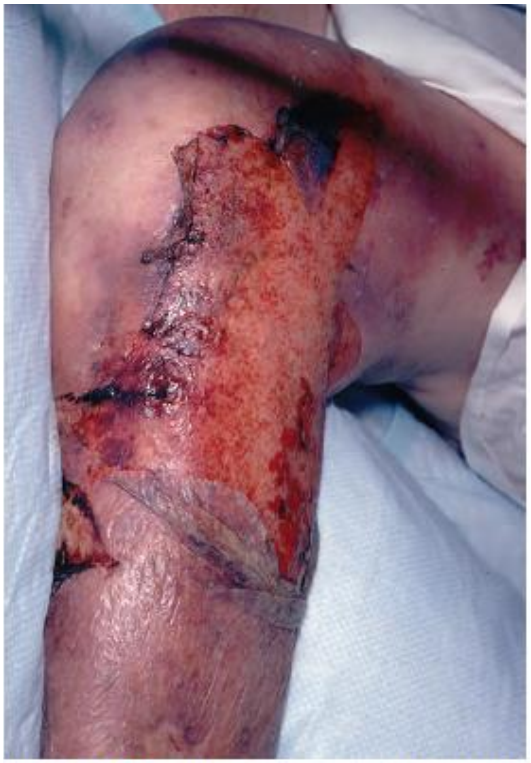


FIGURE 14-45 ■ Toxic epidermal necrolysis. Denuded epidermis becomes dark red with an oozing surface.

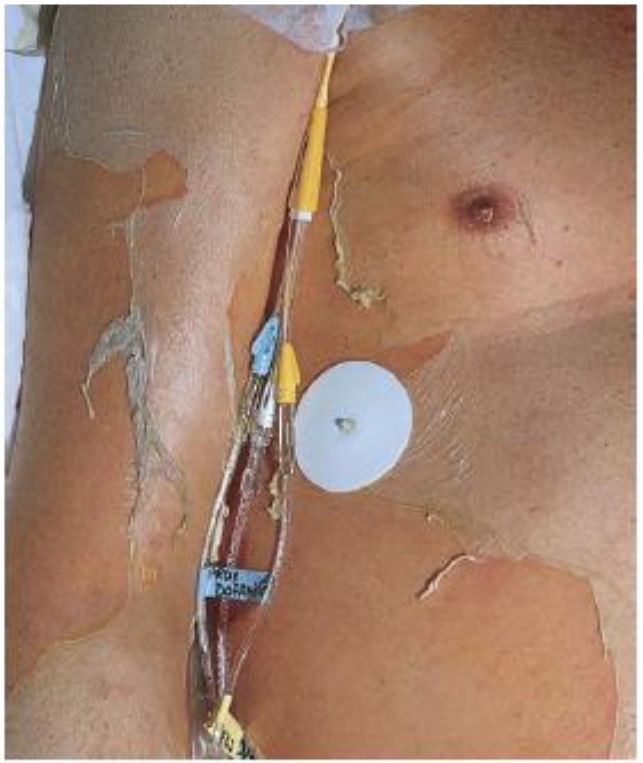
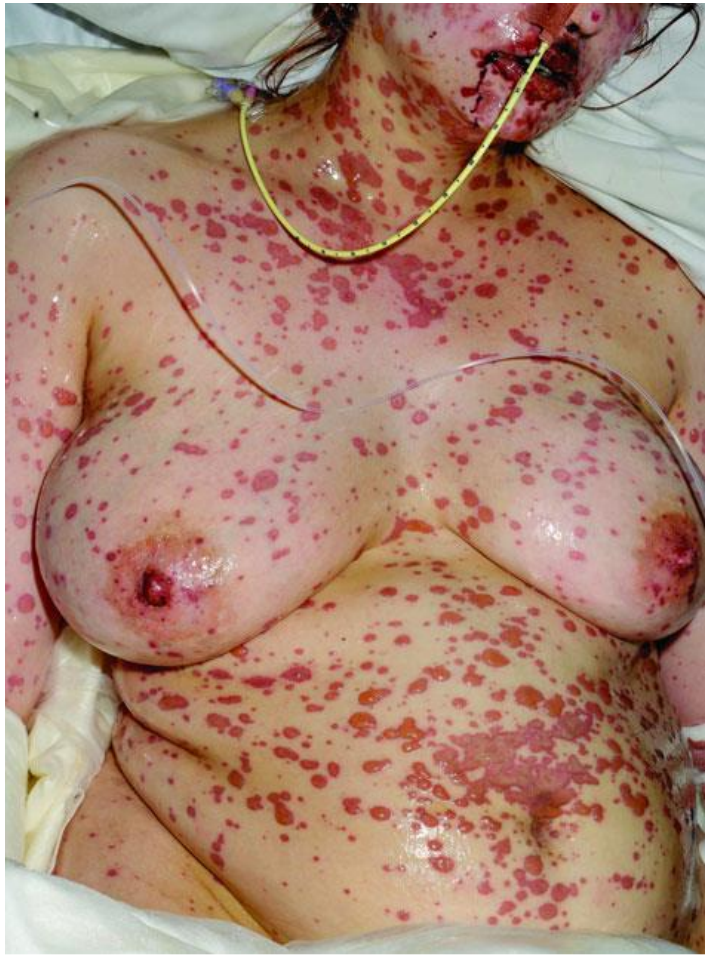
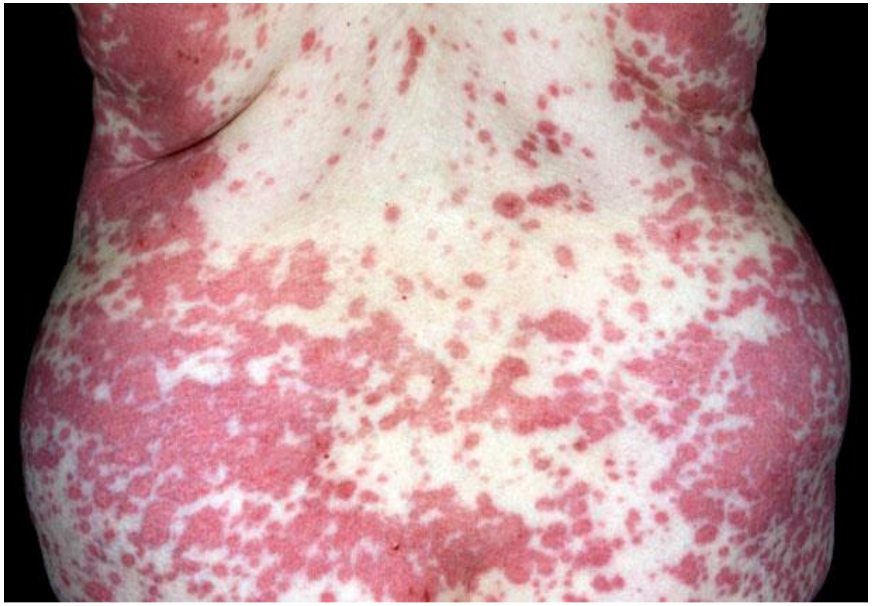
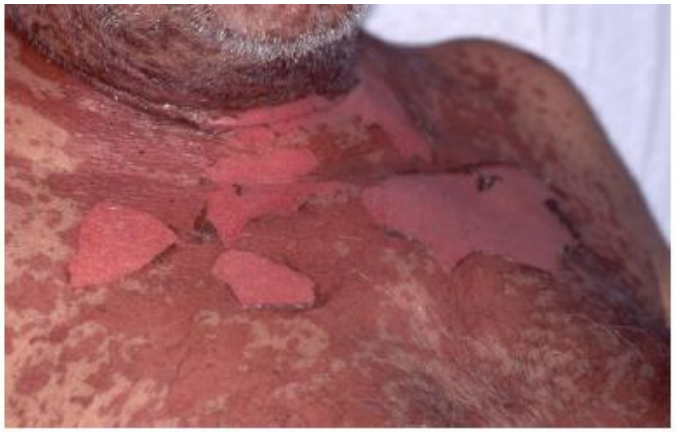


FIGURE 14-46 ■ Toxic epidermal necrolysis. Large sheets of full-thickness epidermis are shed.







. Toxic epidermal necrosis. Patient with denudation
e epidermis in sheets resembling wet cigar paper.
the widespread involvement of the trunk.

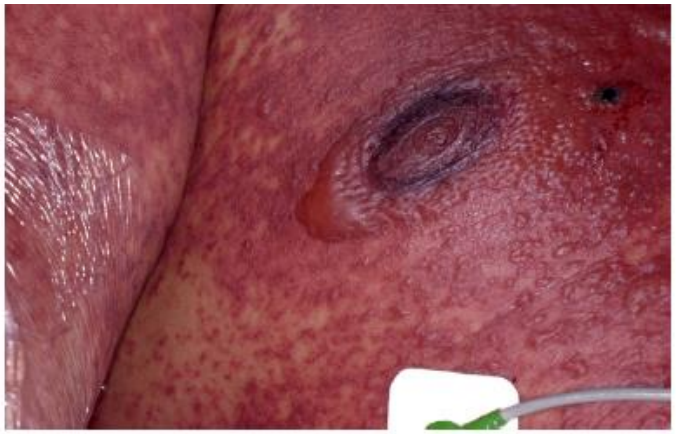
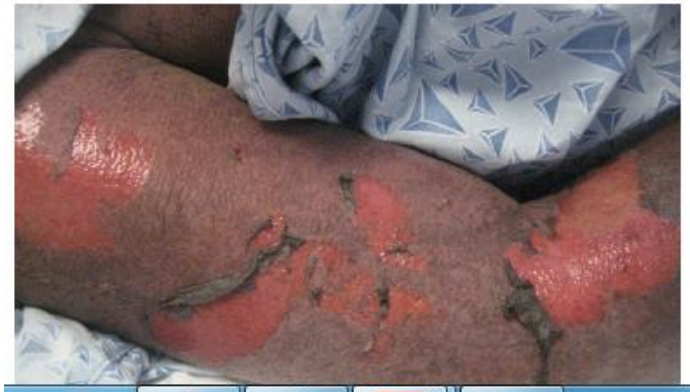
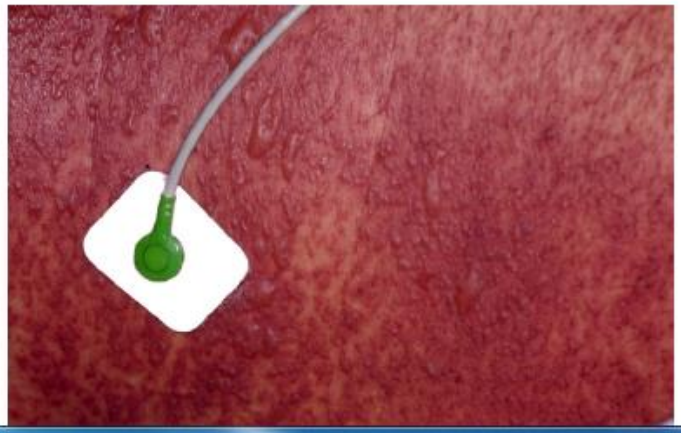
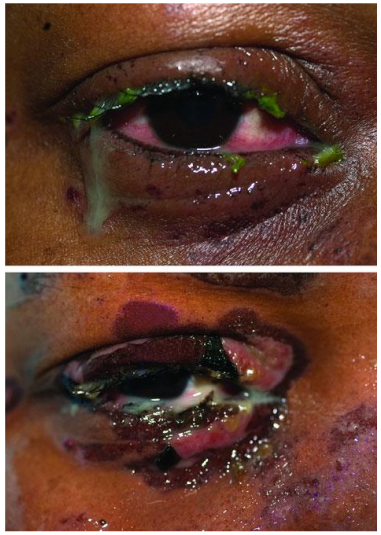
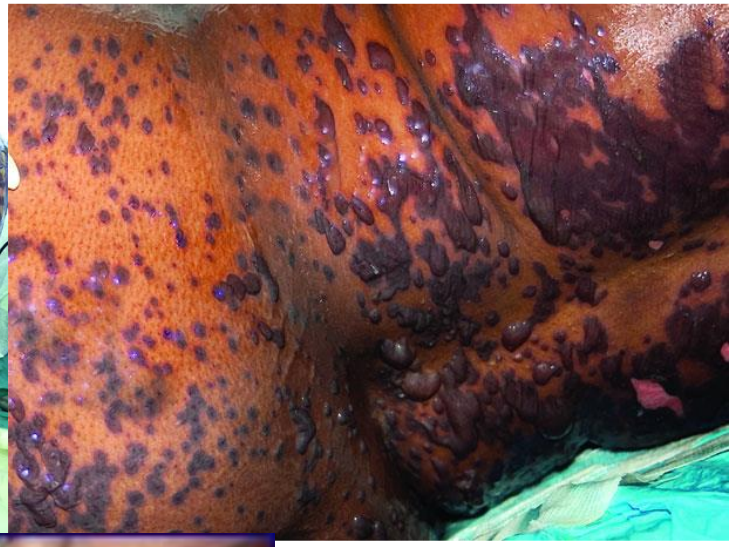
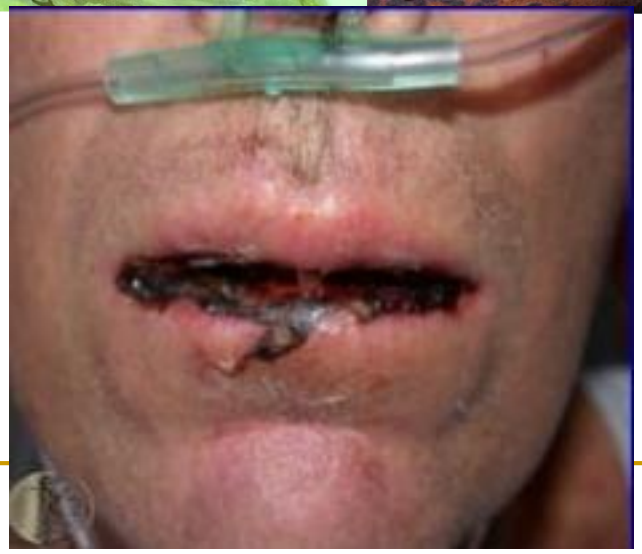


Fig 4. Toxic epidermal necrosis. Extensive blister
erosions involving >30% of the body surface area.





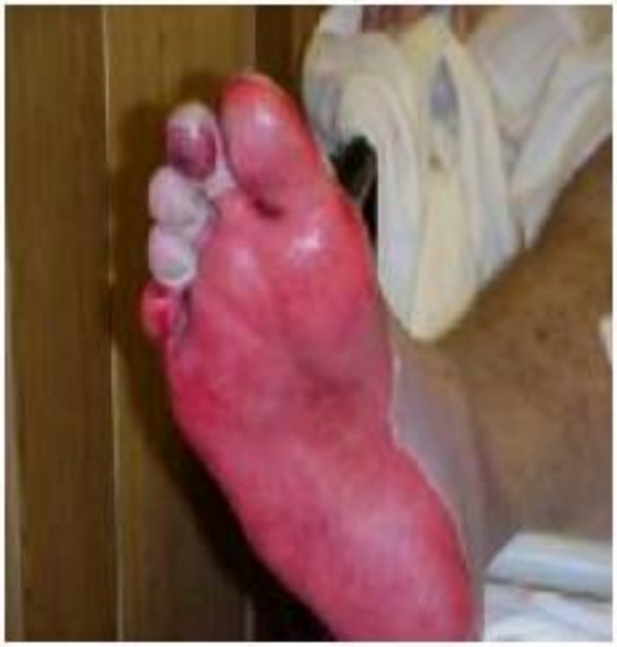


Shedding Skin

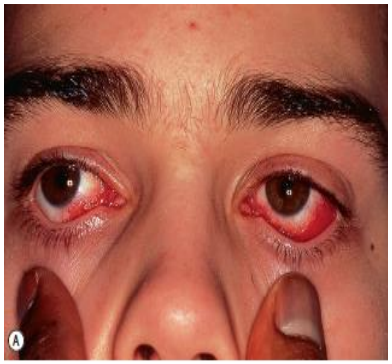
SKIN STARTS SLOUGHING

SKIN COMPLETELY GONE



Mucosal lesions

- Oral mucosa and the vermilion border are almost invariably involved
- Ocular: 80%, the most common change is conjunctivitis with purulent discharge, but bullae may develop. Corneal ulceration is frequent, and anterior uveitis or panophthalmitis may occur
- The eye changes may regress completely, but at least 50% of pts have late eye sequelae including pain, dryness, and scarring and synechiae between the eyelids and conjunctiva



Laboratory abnormalities

- Anemia and lymphopenia, common
- Eosinophilia is unusual
- Neutropenia in about 1/3 of patients, correlated with poor prognosis
- Hypoalbuminemia, electrolyte imbalance, and increased BUN and glucose in severe cases,
- Mild elevations in serum aminotransferase levels (two to three times) in about 50% of pts, overt hepatitis in 10%

COMPLICATIONS

- Electrolyte imbalance
- hypovolemic shock with renal failure
- Bacteremia
- Insulin resistance
- Hypercatabolic state
- Multiple organ dysfunction syndrome
- Sepsis and septic shock, most often caused by *S. aureus* and *P. aeruginosa,* are the main cause of death in these patients
- 1/3 of positive blood cultures enterobacteriae
- Central IV lines are a source for infection and should be avoided in favor of peripheral lines

COMPLICATIONS

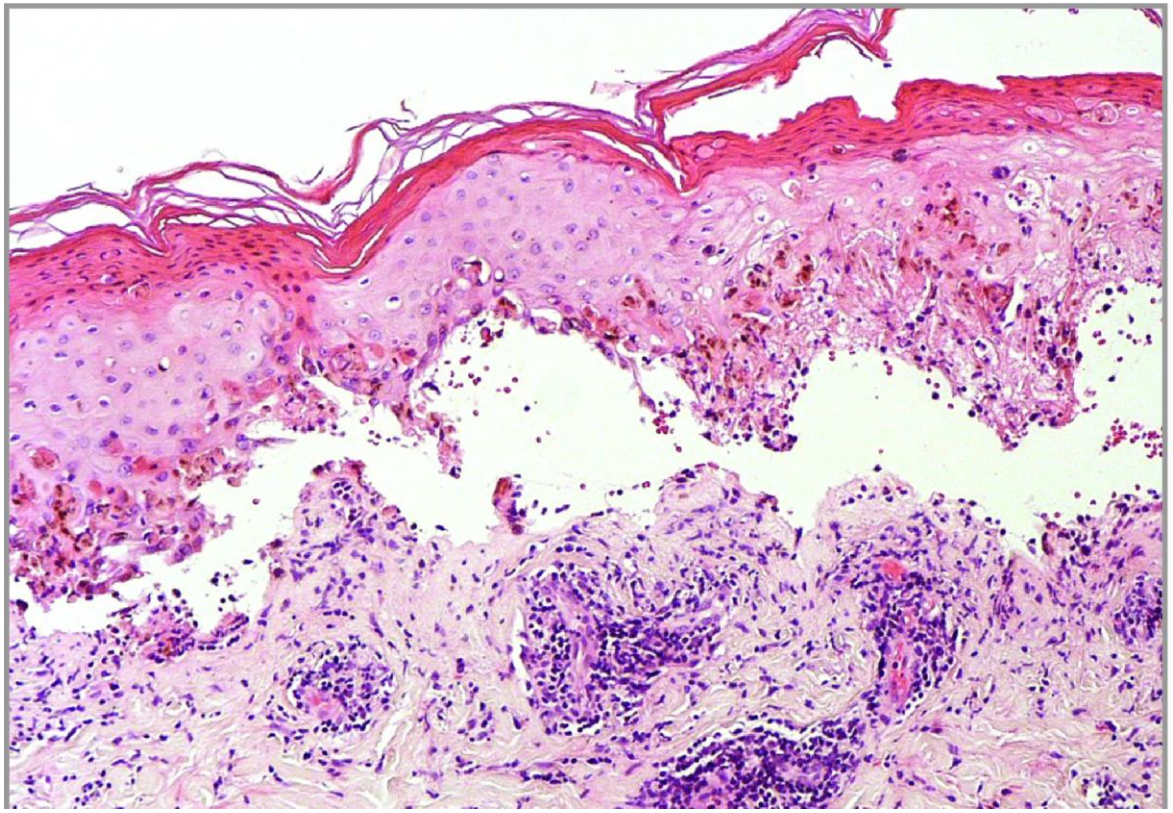
- Pulmonary complications: pneumonia, interstitial pneumonitis
- ARDS in 25% of pts with SJS/TEN
- Diarrhea, melena, small bowel ulcerations, colonic perforation, and small bowel intussusception have been reported in a few patients

PATIENT EVALUATION AND DIAGNOSIS

- History of drug or febrile illness: for the first time 1-4w (average 14d), but in reexposure in as little as 48 hours
- Prodrome of acute-onset febrile illness and malaise
- Painful rash
- Erythematous macules, targetoid lesions, or diffuse erythema progressing to vesicles and bullae
- Positive Nikolsky sign
- Painful mucosal erosions
- Necrosis and sloughing of the epidermis

Skin biopsy

large (>4 mm) punch biopsy or a deep shave biopsy (saucerization)



Laboratory and imaging studies

- CBC, glucose, electrolytes, BUN, Cr,Ca, total protein, albumin, LFT, ESR, CRP
- Bacterial and fungal cultures from blood, wounds, and mucosal lesions
- In children, PCR and/or serologies for *M. pneumoniae* in the early stage of disease and 3 weeks later
- CXR

TEN SCORE

Criteria: 1 point per condition
Age >40 years
Heart rate >120 beats per minute
Comorbid malignancy
Epidermal detachment >10% body surface area on day 1
Blood urea nitrogen >28 mg/dL
Glucose >252 mg/dL
Bicarbonate <20 mEq/L
Total score (mortality rate)
0-1 (3.2%)
2 (12.2%)
3 (35.5%)
4 (58.3%)
≥5 (90.0%)

*Data from Bastuji-Garin et al.[4]

Referral

- SCORTEN 0-1: nonspecialized wards
- detachment >30% **and** a SCORTEN ≥2: ICU, burn units

Wound care

- 1-Surgically débridment
- 2-Antishear wound care
- Equivalent rates of survival and re-epithelialization (uptodate)
- More conservative wound care that minimizes or avoids shear stress on wounds, and leaves skin intact, was associated with better survival and re-epithelialization
- Nonadherent nanocrystalline gauze
- Biosynthetic skin substitutes (eg, Biobrane, Aquacel AG, Suprathel) have also been used successfully

Wound care

- Castillo et al. review of 22 studies of different dressing in TEN/SJS
- No significant difference was in healing time between simple older style dressings such as ointment with bandages and modern biosynthetic and silver impregnated dressings
- Modern dressings could be left in place for longer faciliating patient comfort

Sterile handling

- Sterile handling and reverse-isolation procedures
- Antiseptic solutions containing octenidine, polyhexanide (eg, Octenisept, Lavasept, Prontosan), or chlorhexidine or silver nitrate
- Silver sulfadiazine should be avoided if SJS/TEN is suspected to be caused by sulfonamides, but silver nitrate and silver-nanocrystalline gauze are safe

Fluids and nutrition

- Replacement volumes are approximately one-third lower than those needed for burn
- Fluid requirements during the first 24 hours may be accurately determined by using the formula: 2 mL/kg of body weight multiplied by percentage skin detachment
- Room temperature: 30 to 32°C

SYSTEMIC STEROIDS

Sheneck 2008	Retrospective	Benifit	prednisone 1-2 mg/kg/d for 3-5d within 24-48 hr	EuroSCAR
Sekula 2013	Cohort	No benifit		RegiSCAR
Roujeo 2011	Systematic review	No benifit		
DEL MAGANA 2011	Systematic review	No deaths	CHILDREN	
Lee 2012	Case controll	No benifit		
Zimmerman 2017	Systematic review	Benifit		
Hirahara 2013	Case series	Benifit	Pulse steroids	
Tsung yu2020	systematic review and MA	No benifit		
Torres	systematic review	No benifit		

IVIG +

- several studies that had showed improved survival among SJS/TEN patients who were treated with high-dose IVIg(2 g/kg or more) high doses

- MoriciMV,GalenWK, ShettyAK, Lebouef RP, Gouri TP, Cowan GS, et al. Intravenous immunoglobulin therapy for children with Stevens-Johnson syndrome. J Rheumatol. 2000;27(10):2494–7.
- 89. Trent J, Halem M, French LE, Kerdel F. Toxic epidermal necrolysis and intravenous immunoglobulin: a review. Semin Cutan Med Surg. 2006;25(2):91–3.
- 90. Prins C, Vittorio C, Padilla RS, Hunziker T, Itin P, Forster J, et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. Dermatology. 2003;207(1):96–9.
- 91. Metry DW, Jung P, LevyML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. Pediatrics. 2003;112(6 Pt 1):1430–6.

Roujeau 2011	Systematic review	Benifit	
Huang 2012	systematic review and meta-analysis	high dose IVIg had a decreased mortality compared with low-dose IVIg	
Lee 2013	Retrospective	Mortality was similar among <3 g/kg and ≥3 g/kg	
Barron 2015	meta-analysis	No benifit	
Zimmermann2017	systematic review and meta-analysis	No benifit	
Tsung yu2020	systematic review and meta-analysis	No benifit	
Torres Navaro2020	systematic review and meta-analysis	No benifit	

IVIG adverse effects

- Nephropathy, hemolysis , thrombosis
- increased risk in high-doses, elderly, and preexisting renal or cardiovascular disorders.

IVIG+ steroids

Jagadeesan2013	prospective	Benifit	
Zhu 2012	Retrospective	Benifit	
Ye 2016	Meta-analysis	No benifit	
Sheneck 2008	Retrospective	Benifit	EuroSCAR
Michelleti2017	Retrospective	Benifit	
Tsung yu2020	Systematic review and Meta-analysis	Benifit	
Torres Navaro2020	Systematic review and Meta-analysis	Benifit	

IVIG+ steroids +

- A 2020 systematic review (67studies, 2079 pts) revealed that none of the adjuvants reduced mortality rate.
- Systemic steroids + IVIg therapy was the only treatment with significant survival benefits
- Cyclosporine and etanercept are promising therapies but more studies are required to provide clearer evidence

J Am Acad Dermatol. 2020 Sep 5;S0190-9622(20)32586-X. doi: 10.1016/j.jaad.2020.08.122. Online ahead of print.

Treating toxic epidermal necrolysis with systemic immunomodulating therapies: a systematic review and network meta-analysis

Tsung-Yu Tsai [1], I-Hsin Huang [2], Yuan-Chen Chao [3], Hua Li [4], Tyng-Shiuan Hsieh [3],

IVIG+ steroids

- A 2020 systematic review and meta-analysis (38 studies,1827 pts) demonstrated that cyclosporine, and IVIG + steroid, might improve mortality
- lower mortality may be due to an improvement in supportive treatment rather than to the benefit of any active treatment.

› J Eur Acad Dermatol Venereol. 2020 Jun 17. doi: 10.1111/jdv.16685. Online ahead of print.

Systemic therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: a SCORTEN-based systematic review and meta-analysis

I Torres-Navarro [1], Á Briz-Redón [2], R Botella-Estrada [1 3]

CYCLOSPORIN

Ng 2018	Metanalysis	Benifit	
Chen 2017	systemic review and meta-analysis	Benifit	
St John 2017	Case series	Benifit	
Tsung yu2020	systematic review and meta-analysis	?	
Torres Navaro2020	systematic review and meta-analysis	Benifit	

3 mg/kg/day for 10 d

TNF-a inhibitors- Infliximab +

- In case reports, 5 mg/kg of infliximab immediately halted the progression of skin detachment and induced re-epithelization within 2–10 days

- Scott-Lang V, Tidman M, McKay D. Toxic epidermal necrolysis in a child successfully treated with infliximab. Pediatr Dermatol. 2014;31(4):532–4.
- Patmanidis K, Sidiras A, Dolianitis K, Simelidis D, Solomonidis C, Gaitanis G, et al. Combination of infliximab and high-dose intravenous immunoglobulin for toxic epidermal necrolysis: successful treatment of an elderly patient. Case Rep Dermatol Med. 2012;2012:915314.
- Fischer M, Fiedler E, Marsch WC,Wohlrab J. Antitumour necrosis factor-alpha antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. Br J Dermatol. 2002;146(4):707–9.
- Hunger RE, Hunziker T, Buettiker U, Braathen LR, Yawalkar N. Rapid resolution of toxic epidermal necrolysis with anti-TNF-α treatment. J Allergy Clin Immunol. 2005;116(4):923–4.
- Zarate-Correa LC, Carrillo-Gomez DC, Ramirez-Escobar AF, Serrano-Reyes C. Toxic epidermal necrolysis successfully treated with infliximab. J Investig Allergol Clin Immunol. 2013;23(1):

TNF-a inhibitors-Etanercept +

- Other case reports have shown a benefit from a single 50-mg subcutaneous injection of etanercept

- Paradisi A, Abeni D, Bergamo F, Ricci F, Didona D, Didona B. Etanercept therapy for toxic epidermal necrolysis. J Am Acad Dermatol. 2014;71(2):278–83.

TNF-a inhibitors-Etanercept +

- RCT :ETN decreased mortality rate compared to steroids.More rapid healing and less serious adverse events in ETN compared to steroid group

- Wang CW, Yang LY, Chen CB, Ho HC, Hung SI, Yang CH, et al. Randomized, controlled trial of TNF-alpha antagonist in CTLmediated severe cutaneous adverse reactions. J Clin Invest. 2018;128(3):985–96.

Plasmapheresis

- No difference in mortality, length of stay in hospital, or time to re-epithelialization

- Furubacke A, Berlin G, Anderson C, Sjöberg F. Lack of significant treatment effect of plasma exchange in the treatment of drug-induced toxic epidermal necrolysis? Intensive Care Med 1999; 25:1307.

Plasmapheresis +

- A prospective study: more rapid improvement in their severity of illness score over 20 days compared with the non-plasmapheresis group

- Han F, Zhang J, Guo Q, Feng Y, Gao Y, Guo L, et al. Successful treatment of toxic epidermal necrolysis using plasmapheresis: a prospective observational study. J Crit Care. 2017;42:65–8.

Thalidomide

- Treatment with thalidomide was studied in a randomized placebo-controlled trial of patients with TEN, but the trial was stopped because of increased mortality among those given the active agent

- Wolkenstein P, Latarjet J, Roujeau JC, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. Lancet 1998; 352:1586.

Sequeles

- A large European cohort found that 90% of pts had sequelae 1 yr later
- Psychiatric consultation
- Skin complication: Irregular pigmentation, most frequent sequelae, hypertrophic or atrophic scars rare, eruptive nevi, Alopecia
- Late ophthalmic complications : 20-75%
- Nail changes: 30%
- Mouth sequelae: 33%
- Vulvar and vaginal complications: 25%
- All pts. With TEN : clinical follow-up a few weeks after discharge and 1 year later, by an ophthalmologist and other organ specialist

Re-exposure

- Cross reaction between "aromatic" anticonvulsants (eg, phenytoin, carbamazepine, lamotrigine, phenobarbital)
- Nonaromatic anticonvulsants (eg, valproate, succinimides, benzodiazepines, gabapentin) for patients with a history of SJS/TEN induced by aromatic anticonvulsants, the risk is probably extremely low

Re-exposure

- SJS/TEN due to sulfamethoxazole: avoid other anti-infectious sulfonamides (eg, sulfadiazine, sulfapyridine) but can use thiazide diuretics or sulfonylurea-derived oral antidiabetics

Table V. Common cross-reacting medications that induce toxic epidermal necrolysis

Antiepileptic drugs
Carbamazepine
Phenytoin
Phenobarbital
Antibiotic sulfonamide drugs
Sulfamethoxazole
Sulfadiazine
Sulfapyridine
Sulfamethizole
β-Lactam antibiotics
Cephalosporins
Carbapenems
Penicillins

APPROACH TO THE PATIENT WITH STEVENS–JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS