stevens – Johnson Syndrome & Toxic epidermal necrolysis

By: Dr vilounna sanaphay

Case scenario

- ເດັກຍິງອາຍຸ 11 ປີ
- Admit: 26/8 – 5/9/ 2017
- Chief complaint: ມີຜື່ນຂຶ້ນຕາມໂຕມາໄດ້2ມື້

Present illness

3ມື້ ກ່ອນມາໂຮງໝໍເດັກມີໄຂ້ສູງ, ເຈັບຄໍ, ຕາແດງ ,ບໍ່ມີອາການເຈັບຕາ,ບໍ່ມີອາການປວດຕາມຕົນໂຕ ໄດ້ກິນຢາລົດໄຂ້ແຕ່ອາການໄຂ້ບໍ່ດີຂຶ້ນ

2ມື້ກ່ອນມາໂຮງໝໍມີຜື່ນຂຶ້ນບໍລິເວນຫູ 2ຂ້າງ ແລະມີປາກບວມ

1ມື້ກ່ອນເລີ່ມມີຜື່ນຂຶ້ນເປັນລັກສະນະຕຸ່ມນ້ຳໃສຈາກນັ້ນລາມມາຫາເອິກ ຫຼັງ ແຂນ ແລະຂາ ຈິ່ງມາໂຮງໝໍ

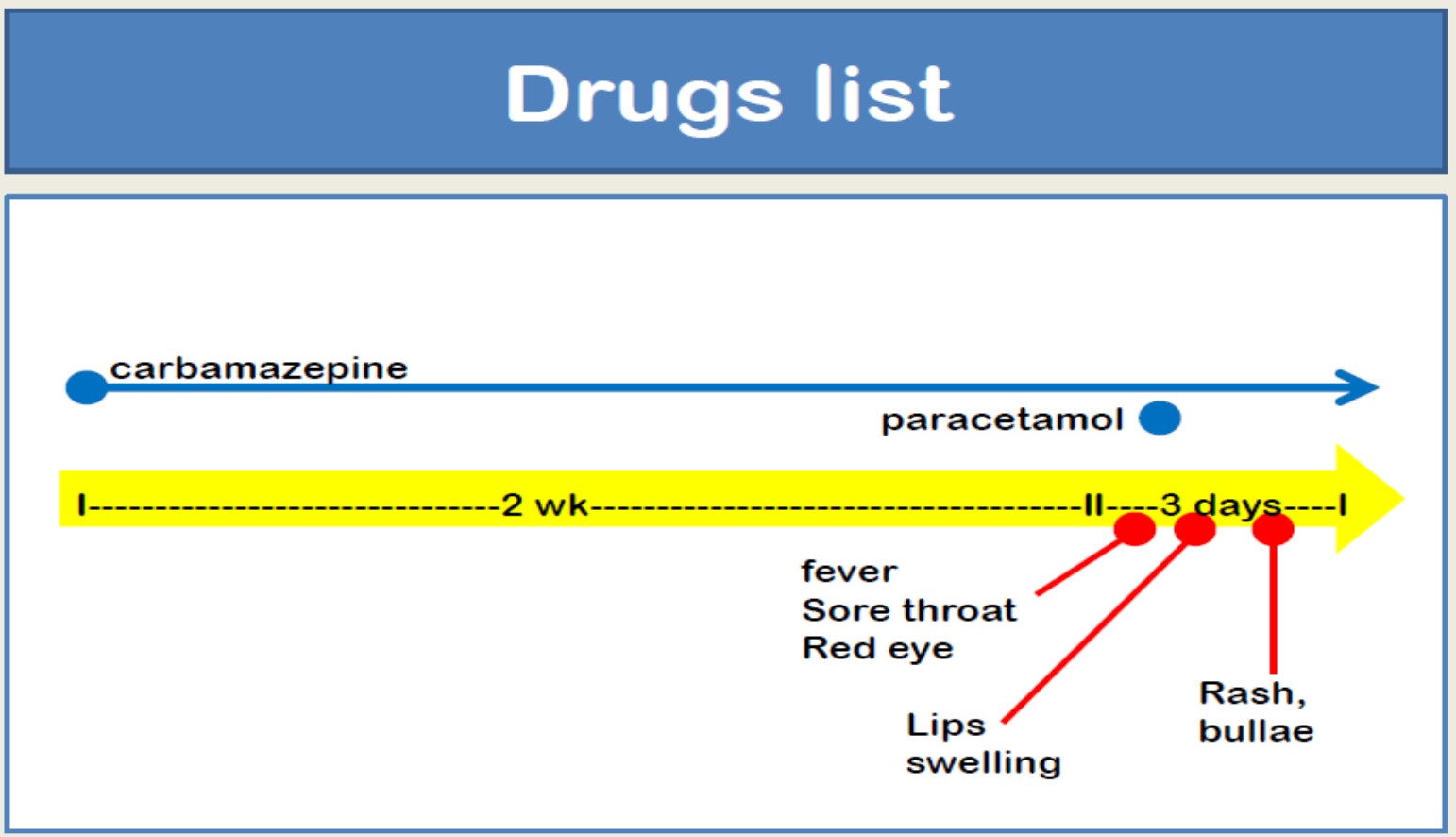
Past History

- Underlying disease : epilepsy (complex partial seizure)

  - ບ່ຶງມະຕິໄດ້ 1ປີຜ່ານມາ ໂດຍຄົນເຈັບມີອາການ ຊັກເກັ່ງໝົດໂຕ ,ມີອາການບໍ່ຮູ້ສຶກໂຕ ແລະ ຢ່ຽວເຮ່ຍເຮັດ, ໄດ້ເຮັດ EEG ພົບມີ epileptic discharge

  - on carbamazepine ½- 1 tab po
- ບໍ່ເຄີຍມີປະຫ້ວດການແພ້ຢາ ແພ້ອາຫານມາກ່ອນ
- ສັກຢາກັນພະຍາດຄົບ
- ພັດທະນາການດີ

Drugs list

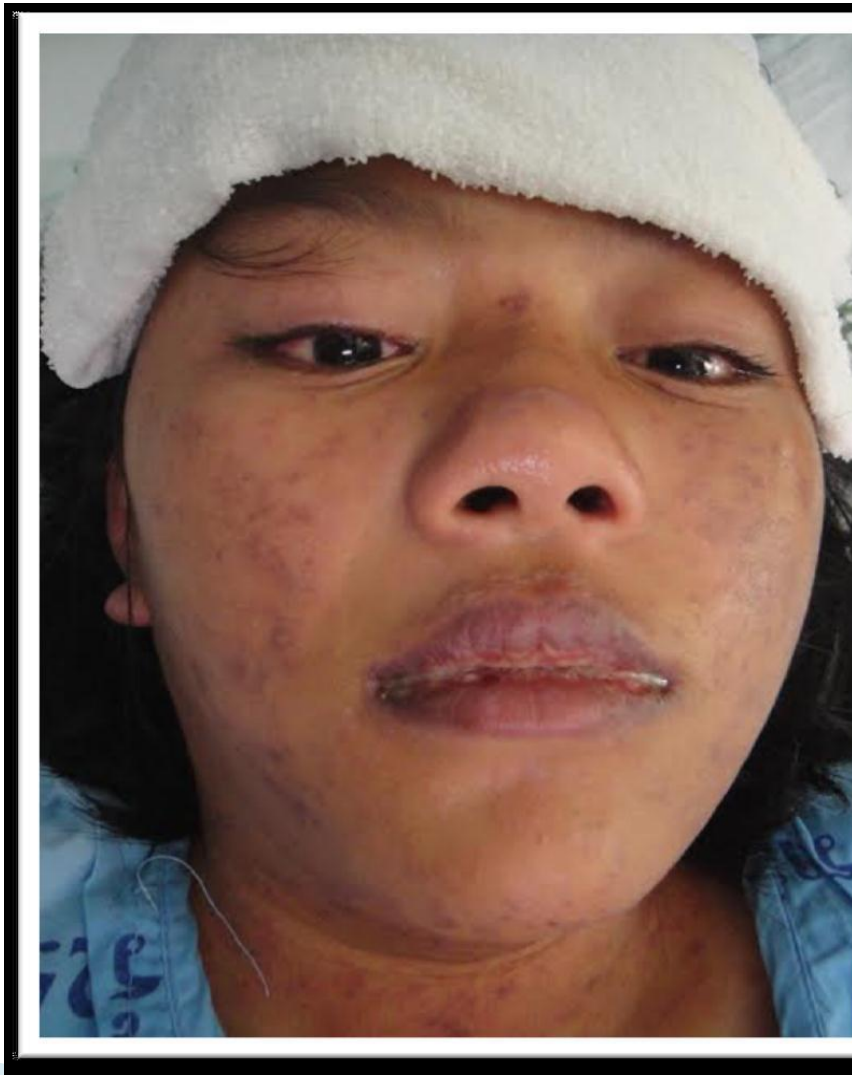

carbamazepine
paracetamol
I----------2 wk----------II----3 days----I
fever
Sore throat
Red eye
Lips
swelling
Rash,
bullae

Physical examination

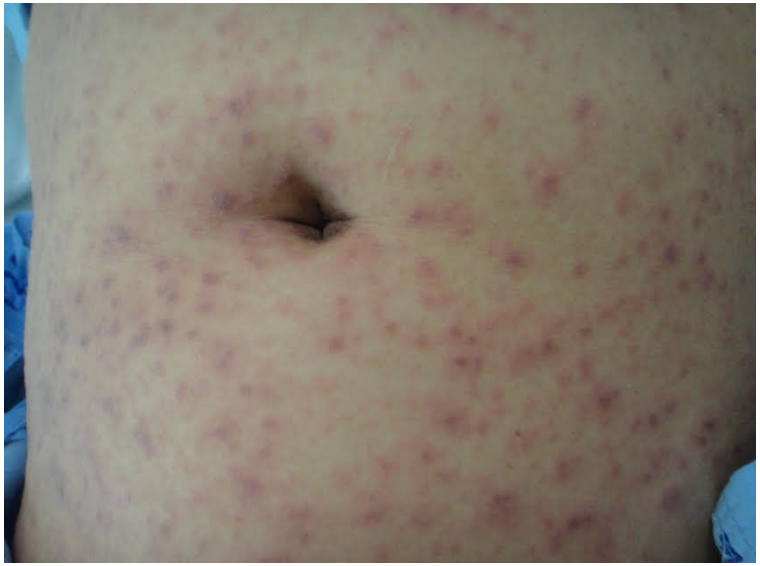
- General apperance : looked drowsy
- Vital Signs: BT 39.9 PR: 125 bpm
  RR 26 tpm BP : 106/72 mmHg
- Body weight: 40kg

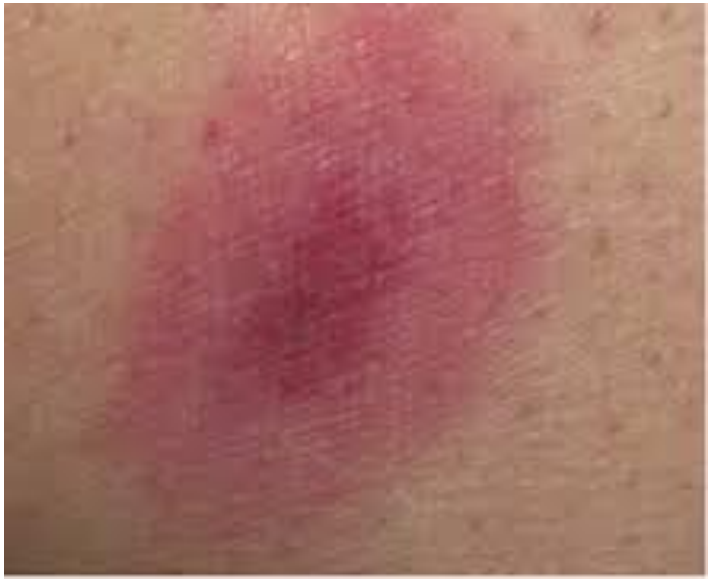
Physical examination

- HEENT :
  - conjunctival hyperemia with pseudomembrane both eyes, no symblepharon
  - no pallor , no jaundice
  - no angioedema
  - lips swelling with blebs and ruptured blebs with pus and serum oozing, marked injected pharynx



- Heart , lungs, abdomen: unremarkable
- Skin :





- Genitalia : no ulcer
- Extremities: capillary refill <2 sce.

Positive findings

- History of new drug administration for 2 weeks
- Skin lesions(-25% BSA)
  - Target – like lesions
    - mucosal involvement (eye, oral mucosa)
- Acute febrile illness

impression : SJS/TEN overlap

Classification

- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, life-threatening mucocutaneous reaction
- Characterized by extensive necrosis and detachment of epidermis

Classification	% of body surface involved
• SJS	< 10%
• SJS/TEN overlap	10-30%
• TEN	>30%

Epidemiology

- Incidence 1-3/1,000,000 persons/year
- ~18% of patients were children
- Pediatric patients usually had less severity of disease than adult patients

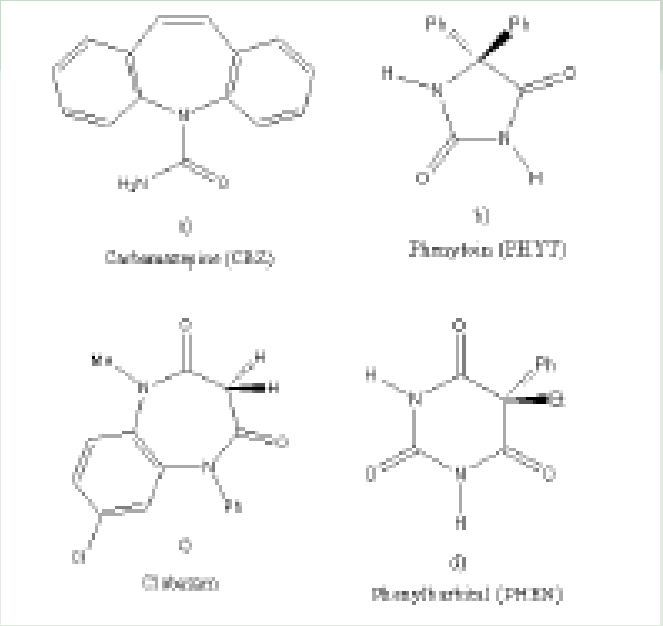
Etiology

- Triggering of the hypersensitivity reaction
  - Drugs (most common)
    - Mycoplasma infection
    - Other infections
  - Neoplasm
  - Autoimmune disorders
  - Vaccination

Etiology : drugs

Box 20-2 Most Common Pharmacologic Triggers of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Allopurinol
Barbiturates
Carbamazepine
Lamotrigine
NSAIDs
Penicillins
Phenytoin
Sulfonamides



Paller, Amy. *Hurwitz Clinical Pediatric Dermatology*. 1st ed. Elsevier, 2016.

Etiology : drugs

Table 1. Comparison of culprit drug between SJS and TEN

Culprit drugs	Total (n=30), n (%)	SJS (n=24)	TEN (n=6)
Antiepileptics (n=18, 60%)	18 (60.0)	15	3
Carbamazepine	8 (26.6)	7	1
Phenobarbital	7 (23.3)	5	2
Phenytoin	2 (6.6)	2	0
Levetiracetam	1 (3.3)	1	0
Antibiotics (n=8, 26.6%)	8 (26.6)	5	2
Erythromycin	3 (10.0)	2	0
Trimethoprim-sulfamethoxasone	2 (6.6)	2	0
Cefotaxime	1 (3.3)	0	1
Cloxacillin	1 (3.3)	0	1
Amoxicillin	1 (3.3)	1	0
Others (n=4, 13.3%)	4 (13.3)	3	1
Aspirin	1 (3.3)	1	0
Brufen	1 (3.3)	1	0
Methotrexate	1 (3.3)	0	1
Paracetamol	1 (3.3)	1	0

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

HLA-B*1502

Techasatian L et al. *World J Pediatr* 2016; online first.

Etiology : Mycoplasma infection

- Less severe disease
- “Mycoplasma pneumonia- induced rash and mucositis “ has been suggested for alternative diagnosis

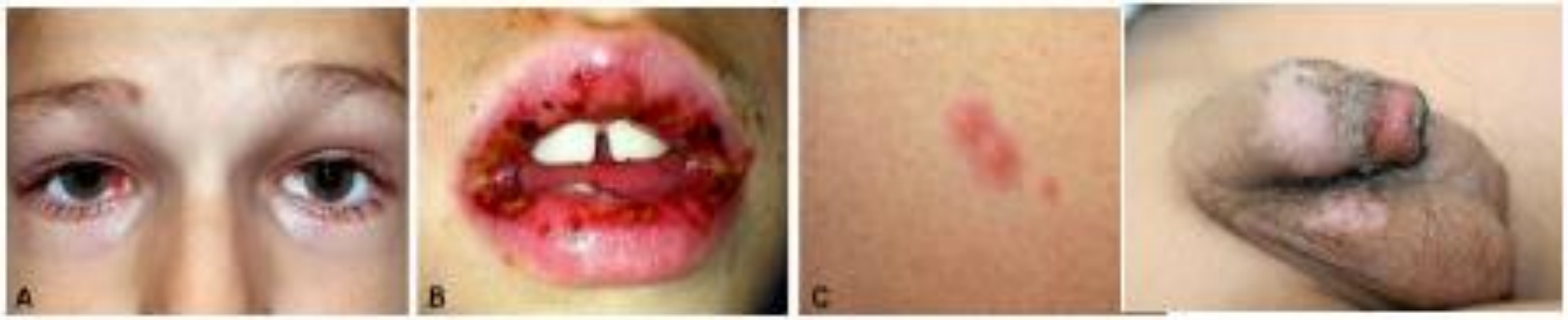
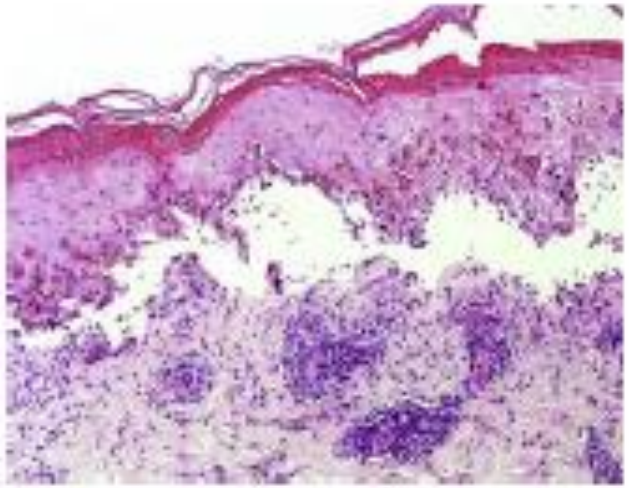


Fig 1. Classic mucocutaneous findings in *Mycoplasma*-induced rash and mucositis (MIRM) cases. Severe conjunctivitis and blepharitis (**A**), severe oral mucositis with hemorrhagic crusting (**B**), and sparse vesiculobullous eruption (**C**). In most cases of MIRM, mucosal involvement is the predominant feature with the cutaneous involvement typically being minimal to sparse.

Fig 2. Genital mucositis in *Mycoplasma*-induced rash and mucositis.

Pathophysiology

- Disorders of keratinocyte death (apoptosis) mediated by cytotoxic T-cell
- Granulysin was found to be the most important cytotoxic mediators
- Other mediators: Fas-Fas ligand, perforin/granzyme



Clinical manifestation

- Occurs 7 to 21 days after the first drug exposure, almost always within 8 wks
- 1 to 14 days prodomal period
- Abrupt onset of
  - high fever
  - varying degrees of generalized targetoid lesions, bullae,epidermal detachment
  - ≥ 2 sites of mucosal erosion

Clinical manifestation

- Constitutional
  - Fever
  - Dehydration
- Mucocutaneous
  - Stomatitis with hemorrhagic crusts
  - Oral and genital erosions
  - Dysphagia
  - Purulent conjunctivitis with photophobia
  - Occasionally esophageal and pulmonary mucosal sloughing
  - Dusky erythematous macules, targetoid lesions, bullae, and skin sloughing
- Visceral
  - Lymphadenopathy
  - Hepatosplenomegaly with hepatitis
  - Uncommonly: pneumonitis, arthritis, myocarditis, and nephritis
- Laboratory abnormalities
  - Increased erythrocyte sedimentation rate (100%)
  - Leukocytosis (60%)
  - Eosinophilia (20%)
  - Anemia (15%)
  - Elevated hepatic transaminase levels (15%)
  - Leukopenia (10%)
  - Proteinuria, microscopic hematuria (5%)

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Cutaneous involvement

- Common areas: face, upper trunk, palms and soles

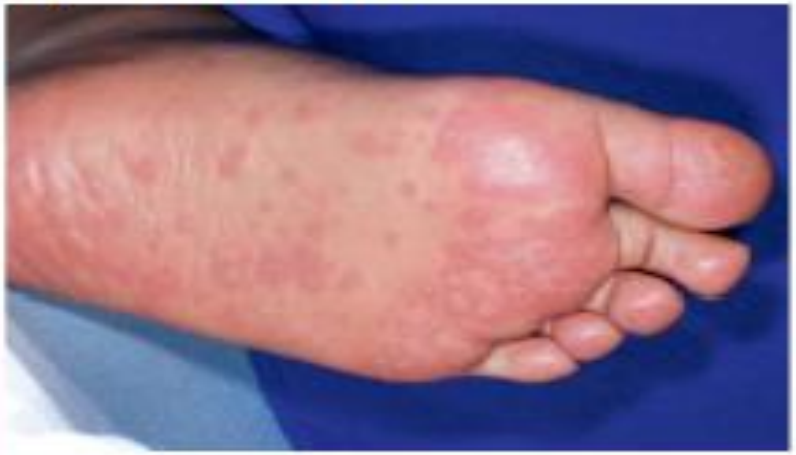

Figure 20-20 Stevens–Johnson syndrome. Note the bullae on the sole in this girl who reacted to lamotrigine.

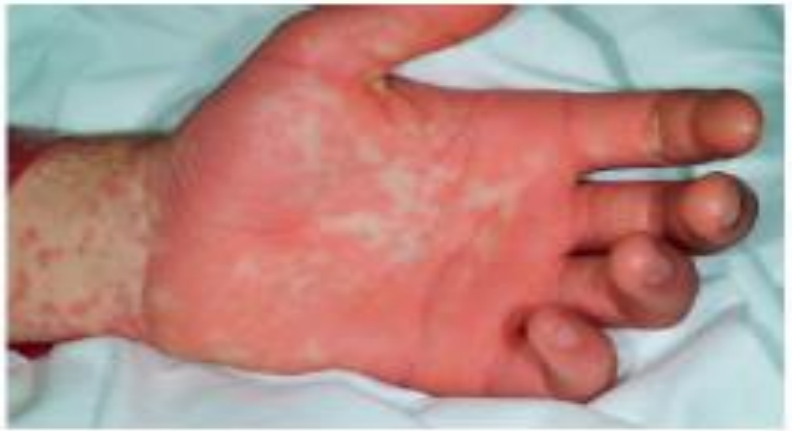

Figure 20-21 Stevens–Johnson syndrome (SJS). Intensely erythematous macules are nearly confluent the palms of this boy with SJS from carbamazepine.

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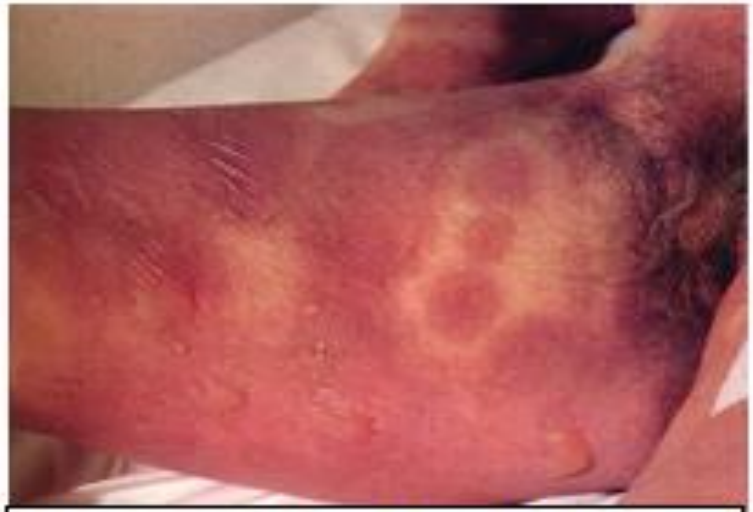
Cutaneous involvement

- Targetoid lesion



Dusky center target-like lesion (SJS)

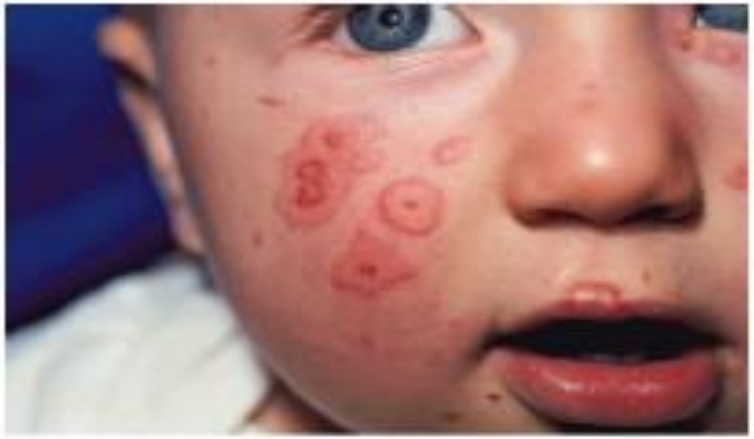


Figure 20-34 Erythema multiforme. Classic target lesions and marginated wheals with central vesicles are characteristic.

Classic target lesion (Erythema multiforme)

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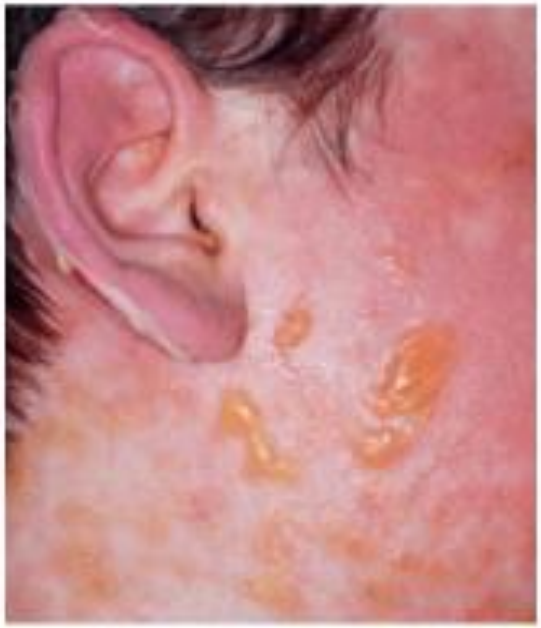
Cutaneous involvement

- Confluent flaccid bullae and skin detachment



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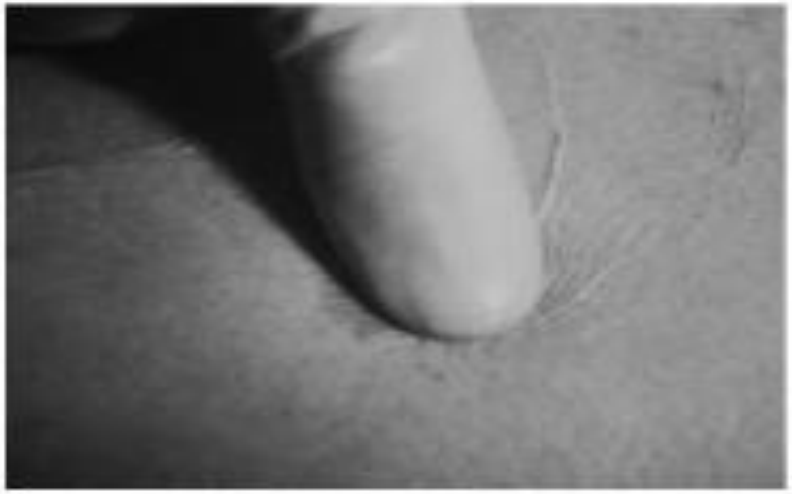
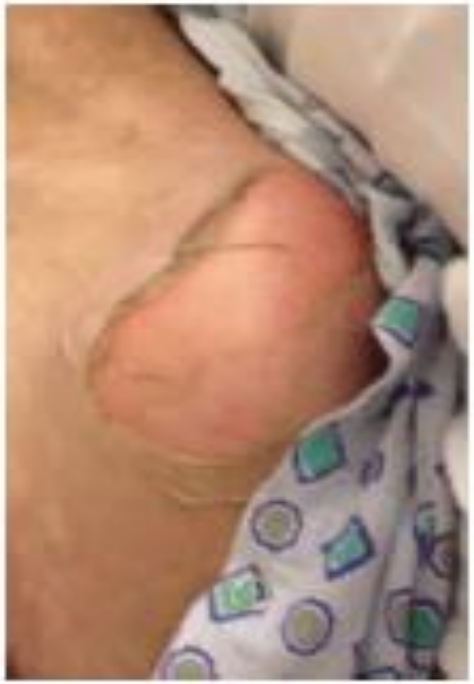
Paller, Amy. *Hurwitz Clinical Pediatric Dermatology*. 1st ed. Elsevier, 2016.

Nikolsky sign

Figure 2. A positive Nikolsky's sign in toxic epidermal necrolysis.



Reproduced with permission from: Habif T, ed. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 3rd ed. St. Louis: Mosby; 1996.



May be seen in other bullous disorders with superficial epidermal detachment (pemphigus, some types of epidermolysis bullosa, SSSS)

Mucosal involvement

- Extensive mucosal involvement is more typical of SJS than TEN
- Occur 1 to 2 days before cutaneous manifestation
- ≥2 affected mucosal surface
  - characteristic hemorrhagic crusts
  - Painful superficial erosions and ulcerations
  - The oral mucosa is always affected

Mucosal involvement

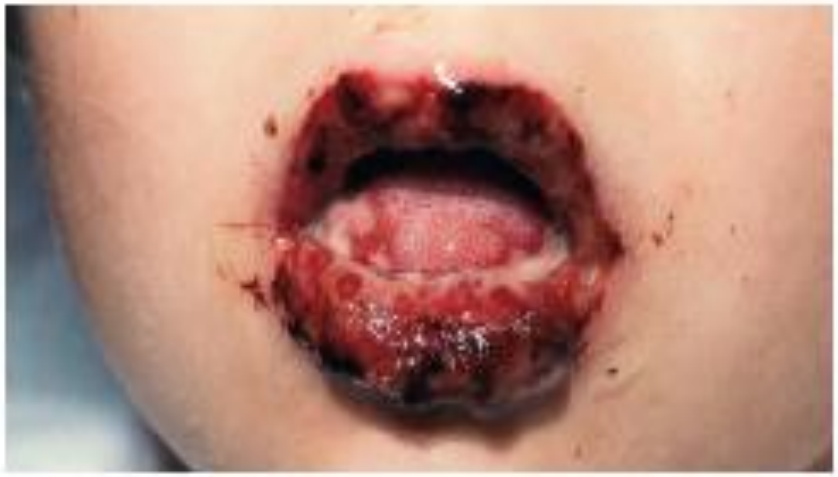


Figure 20-27 Stevens-Johnson syndrome. Mucous membrane involvement with severe swelling and hemorrhagic crusting of the lips.

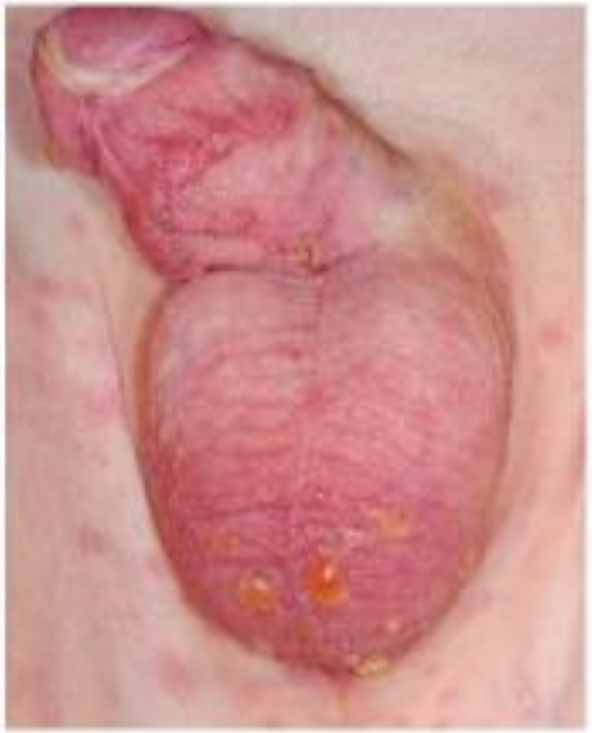


Figure 20-24 Toxic epidermal necrolysis. Note the discrete bullae on the scrotum sloughing of mucosae at the glans. The sloughed skin resembles wrinkled, wet, tissue paper.

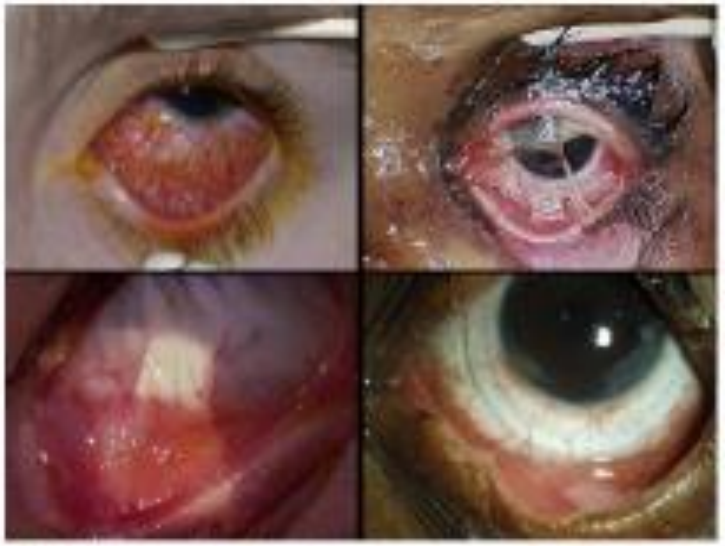
Ophthalmologic manifestation

- Severe purulent conjunctivitis with photophobia
- Corneal ulceration
- Keratitis
- Uveitis
- Panophthalmitis
- Long term sequelae occur in 40% of patients

(keratoconjunctivitis sicca, corneal ulceration, trichiasis, symblepharon, blindness)

Ophthalmologic manifestation

Figure 20-28 Stevens-Johnson syndrome. This boy shows early ophthalmic involvement with conjunctival injection, eyelid edema, erythema, and exudative crusting.



Clinical manifestation : summary

	SJS	SJS-TEN	TEN
Lesional morphology	Tagetoid lesions, dusky red macules, bullae	Tagetoid lesions, dusky red macules, bullae	Tagetoid lesions, dusky erythematous macules and plaques; detachment of epidermis
Localization	May be scattered and isolated; may be confluent, esp on the trunk and face	May be scattered and isolated; often confluent	Usually extensive involvement with widespread confluence
Involved skin	<10%	10%-30%	>30%
Biopsy features	More interface dermatitis	Significant interface dermatitis + necrolysis	Predominantly necrolysis
Mucosal changes	Prominent	Prominent	May be less than in SJS
Systemic involvement	Often present	Always present	Always present

Paller, Amy. *Hurwitz Clinical Pediatric Dermatology*. 1st ed. Elsevier, 2016.

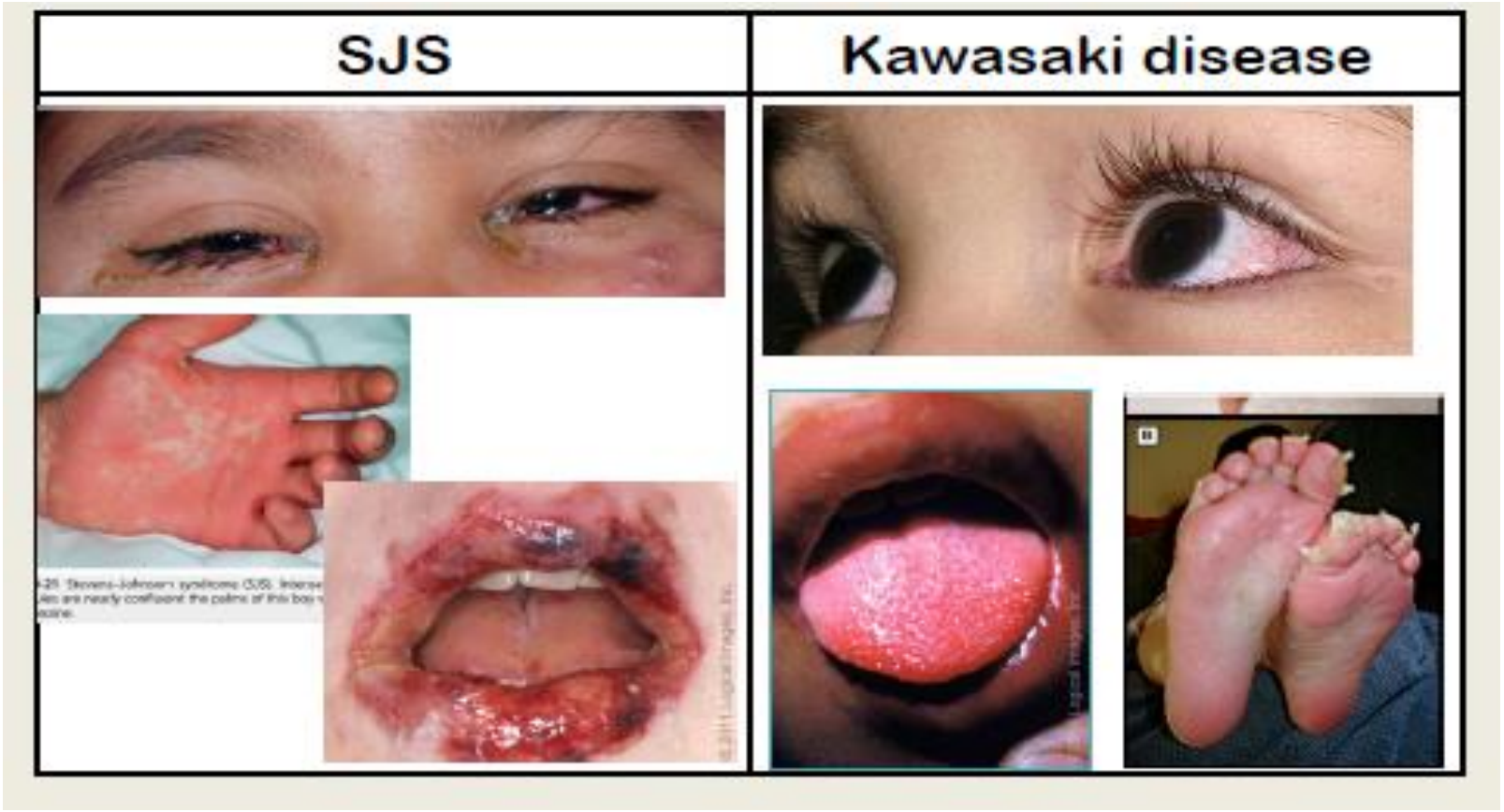
Differential diagnosis

- Kawasaki disease
- Erythema multiforme
- Immunobullous disorders
- Staphylococcal scalded skin syndrome

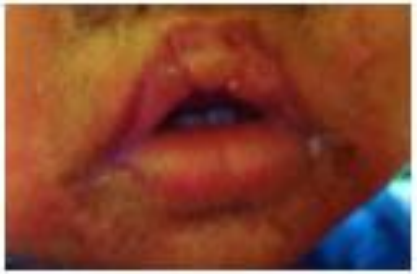
SJS/TEN VS Kawasaki disease

	SJS/TEN	Kawasaki disease
Age (years)	All ages	Usually < 5
Fever	Prolonged	Persistent
Eyes	Exudative conjunctivitis, keratitis	Nonexudative conjunctivitis, limbal sparing, anterior uveitis
Oral mucosa	Erythema, ulceration	Diffused erythema "Strawberry tongue"
Peripheral extremities	Skin detachment in affected areas	Erythema and edema of palms and soles, periungual desquamation
Rash	Targetoid lesions, flaccid bullae	Erythematous, polymorphous; targetoid or purpuric in 20%

SJS/TEN VS Kawasaki disease



SJS/TEN VS SSSS

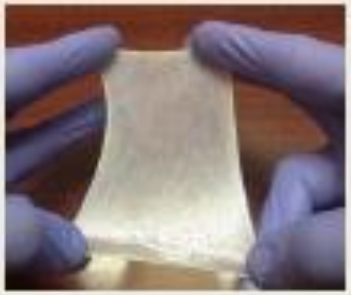
	SJS/TEN	SSSS
Mucosal involvement	Yes 	No 
Distribution	Trunk, palms and soles	Periorificial predominant
Skin lesions	Blistering and skin denudement (panepidermal detachment)	Superficial desquamation 

Management

- Stop drugs
- Admit to ICU or burn unit
- Aggressive supportive care
  - Fluid and electrolytes replacement
  - Intravenous caloric replacement
  - Wound care
  - Vigorous pain control
- Ophthalmologic consultation**

Management : skin care

- Avoid manipulation
- Keep intact areas of skin dry
- Daily cleansing of open wond
- Cover detached areas with non – adherent, moist dressing
-



Pediatrics. 2003 Dec;112(6 Pt 1):1430-6.

Use of intravenous immunoglobulin in children with stevens-johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature.

Metry DW[1], Jung P, Levy ML.

Author information

Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis are the most severe cutaneous reactions that occur in children. Off-label use of human intravenous immunoglobulin (IVIG) has been reported in a number of autoimmune and cell-mediated blistering disorders of the skin, including severe cutaneous drug reactions. We review 28 previous reports in which IVIG was used in pediatric patients with SJS and toxic epidermal necrolysis and discuss our experience in 7 children with SJS, in whom no new blisters developed within 24 to 48 hours after IVIG administration and rapid recovery ensued. IVIG seems to be a useful and safe therapy for children with severe cutaneous drug reactions. Well-controlled, prospective, multicenter clinical trials are needed to determine optimal dosing guidelines and to compare the efficacy and safety of IVIG with other potentially effective modalities.

PMID: 148

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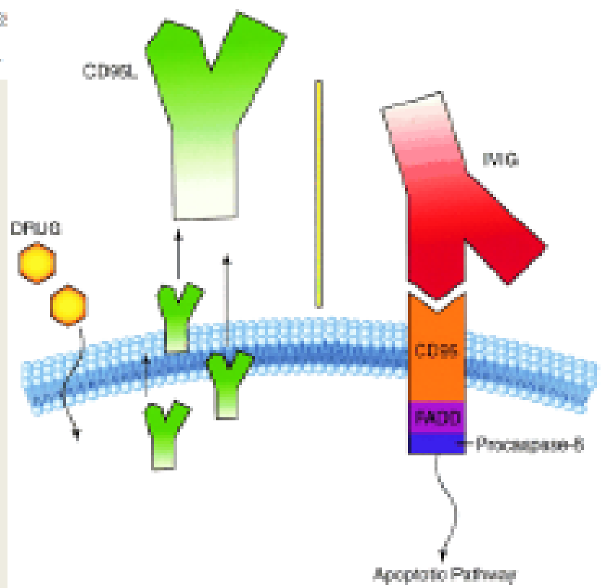

Dose: 0.5-1 g/kg administrated over 3 days

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IV corticosteroids

- In drug-induced SJS/TEN patients, early administration of systemic corticosteroids was shown some benefits in shorting hospitalization

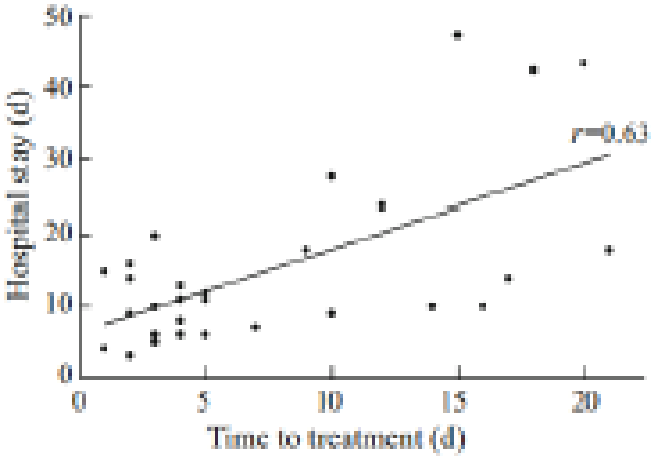


Fig. Spearman correlation between time to systemic corticosteroids treatment and the length of hospital stay.

Techasatian L et al. *World J Pediatr.* 2016; online first.

Complication

- Massive fluid loss and electrolyte imbalance
- Malnutrition
- Bacterial super infection and septicemia
  - Skin infection
  - Pneumonia
  - Urinary tract infection

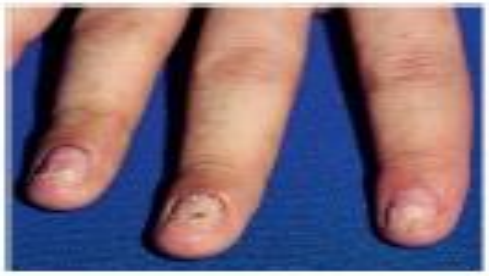
Outcome

- Mortality rate (adult patients)
  - SJS 5%
  - SJS/TEN 10%- 15%
  - TEN 30% - 35%
- Mortality rates in children have been lower
  - Srinagarind Hospital : 5% mortality in pediatric SJS/TEN patients

Paipool W, Sriboonnark L. *Asian Biomed*. 2015;9:193-6

Long term sequelae

- Cutaneous dyschromia (42%)
- Persistent nail dystrophy or anonychia
- Late ocular complications
  - Dry eye syndrome (59%)
  - subconjunctival fibrous scarring (33%)
  - Corneal erosions(29%)
  - Others (<25%): trichiasis, symblepharon, visual loss



Back to case scenario ..

- Diagnosis:

  SJS/TEN overlap

Management

- " Discontinued suspected Medication"
- Skin care
  - Wet dressing wound and lips
  - Drainage bled ' but not unroof'
  - Hygiene mouth care
  - Tropical Antibiotic : Fucidin ointmet apply abraded skin bid
- Systemic corticosteroids
  - Dexamethasone 4mg IV q 6hr x 5 days

Management

- IV fluid rehydration
- Nutritional support
  - Panenteral (1:1) 400ml po x 4 feeds (1600kcal/day)
- Control Pain
  - IV morphine

Management

- **Eye care : consult ophthalmologist**
  - **Remove Pseudomembrane**
  - **Moisture**

    Tear natural free apply both eyes q 1hr >> vislube both eyes q 1hr

    Vidisic gel both eyes bid>> Genteal gel apply both eyes bid
  - **0.1% Dexamethasone Eye drop both eyes qid**
  - **Antibiotic : Chloramphenicol Eye ointment apply both eyes qid , Fusithalmic eye ointment apply abraded eyelids**

Take home message

- Diagnosis of SJS/ TEN
  - History of new drug administration
  - skin lesion (target –like ,bullous)
  - ≥ 2 mucosal involvement
- Management
  - Immediately discontinue all suspected drugs
  - Early ophthalmolohists consultation for proper eyes care to prevent late complications

References

Paller, Amy. *Hurwitz Clinical Pediatric Dermatology*. 1st ed. Elsevier, 2016.

Techasatian L et al. Drugs-induced Steven-Johnson syndrome and toxic epidermal necrolysis in children: 20 years study in a tertiary care hospital. *World J Pediatr.* 2016; online first.

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many
Thanks!