藥品相關皮膚不良反應之臨床診斷與治療策略-以抗生素為例

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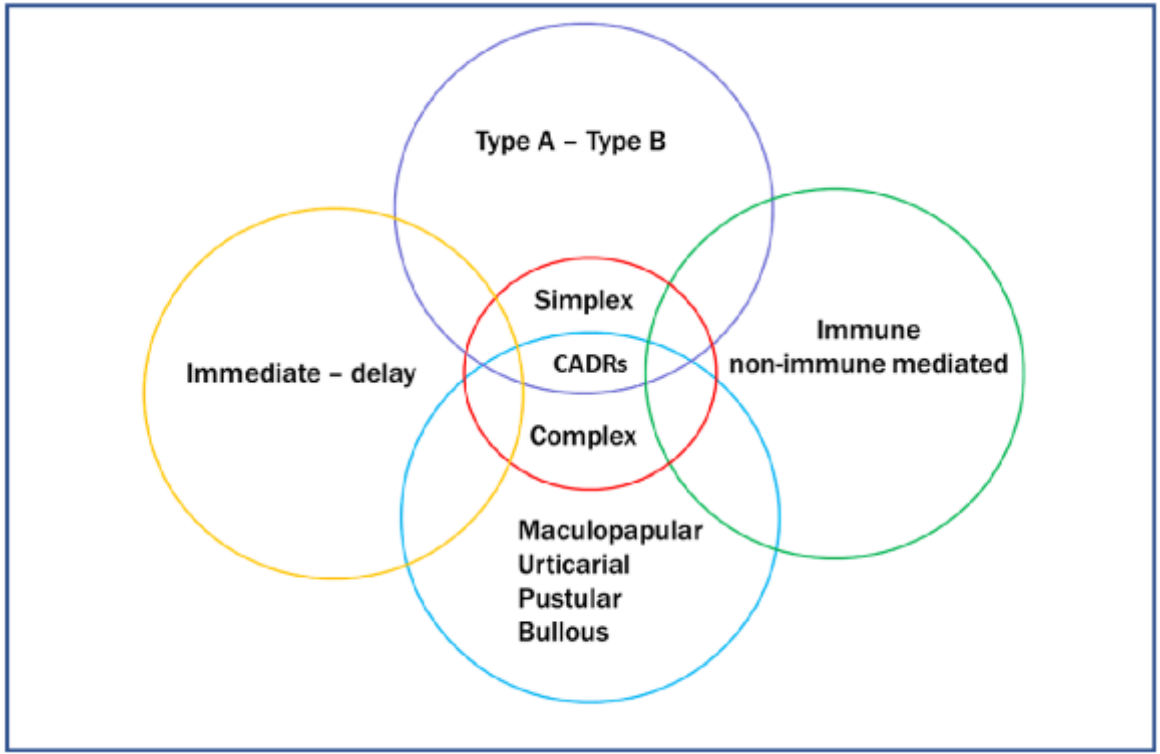
2025/10/08

Cutaneous adverse drug reaction (CADR) classification types



Br J Clin Pharmacol. 2024;90:1838–1855

Drug-induced skin disease or cutaneous adverse drug reactions (CADRs)

- Drug-induced skin disease or cutaneous adverse drug reactions (CADRs) are terms that encompass the clinical manifestations of the skin, mucosae and adnexa induced by a drug or its metabolites.
- The skin is the organ most frequently affected by drug reactions, which may affect up to 10% of hospitalized patients and occur in 1–3% of multimedicated patients.
- Most CADRs are mild or self-resolving conditions; however, 2–6.7% of could develop into potentially life-threatening conditions.

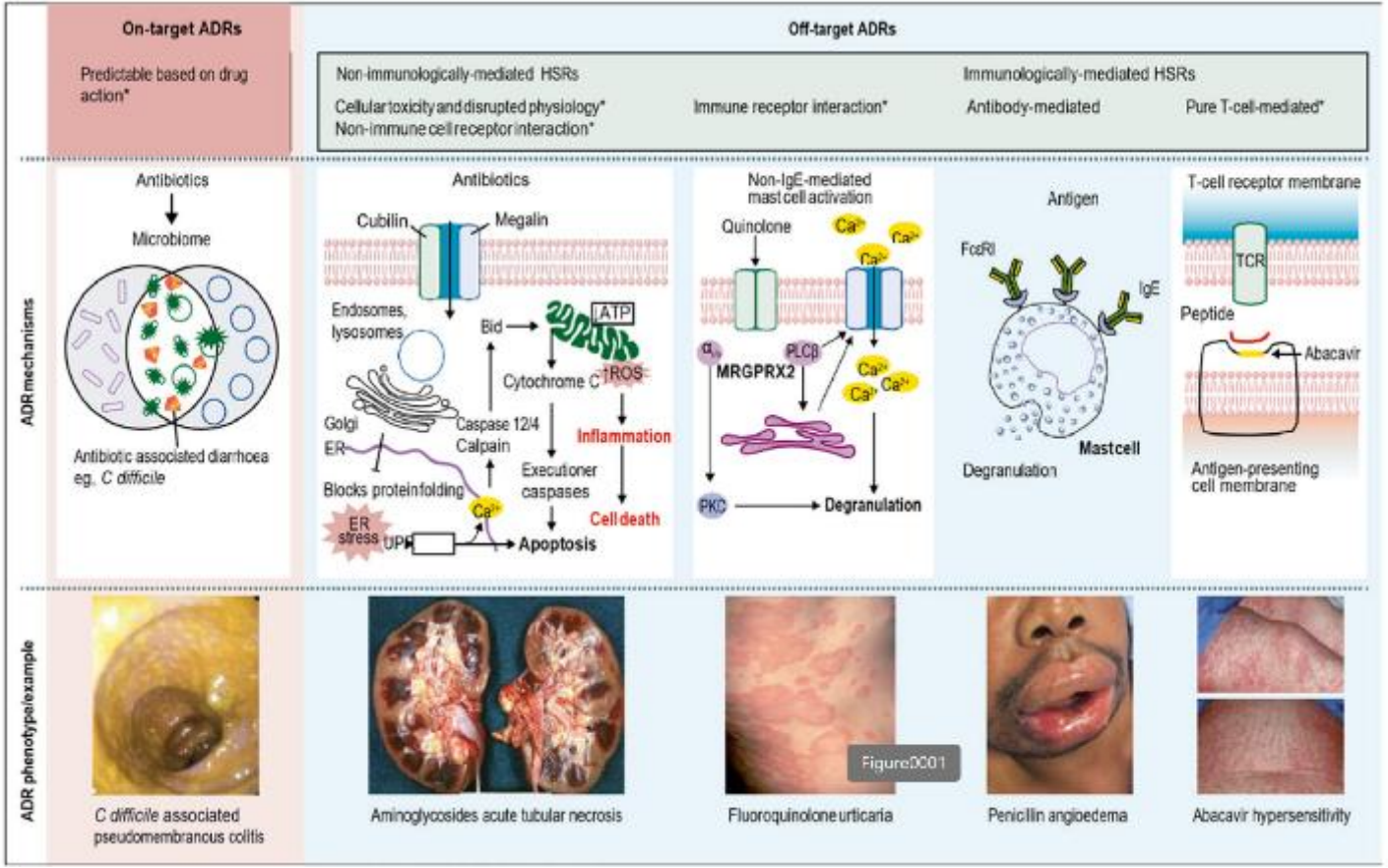
Br J Clin Pharmacol. 2024;90:1838–1855

Cutaneous adverse drug eruptions

- Type A reactions: are predictable, dose-related toxicities, often identified in preclinical or clinical trials, and usually occur in overdose settings.
- Type B ADRs: predominantly T cell-mediated drug-induced delayed hypersensitivity reactions (DHRs), presents variable severity and clinical diagnosis, from mild skin injury such as maculopapular exanthema (MPE) to life-threatening severe cutaneous adverse drug reactions (SCARs) including acute generalized exanthematous pustulosis (AGEP), drug reactions with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

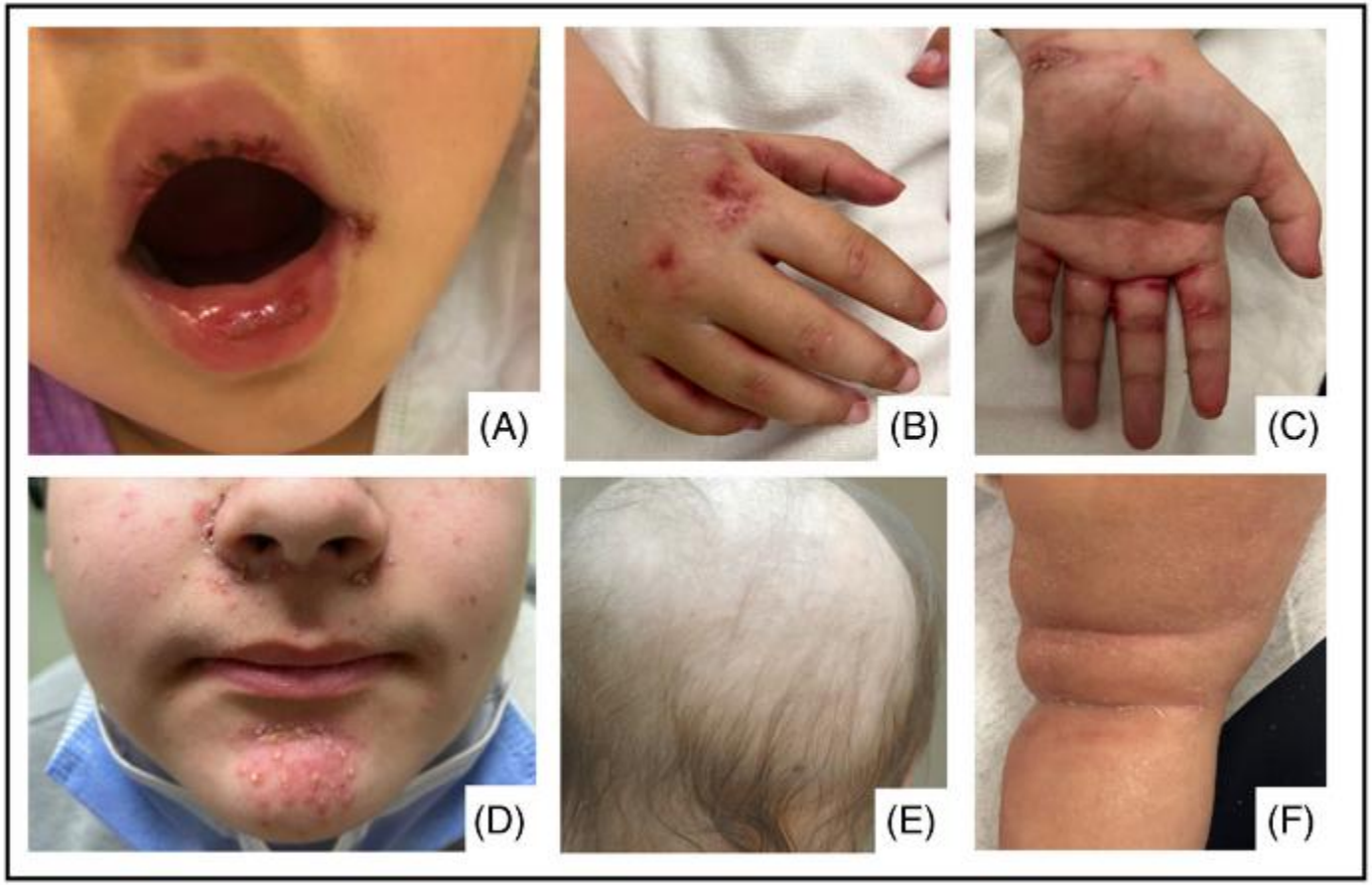
Front Pharmacol. 2023 Apr 26;14:1183491.

Classification of on-target and off-target ADRS Pink panel illustrates an example of an on-target ADR



Lancet. 2019 January 12; 393(10167): 183–198.

Type A reaction



A) Mucositis due to methotrexate, B and C) Hand foot syndrome, D) Acneiform eruption due to trametinib, E) Alopecia due docetaxel, F) Eczematous eruption due to trametinib.

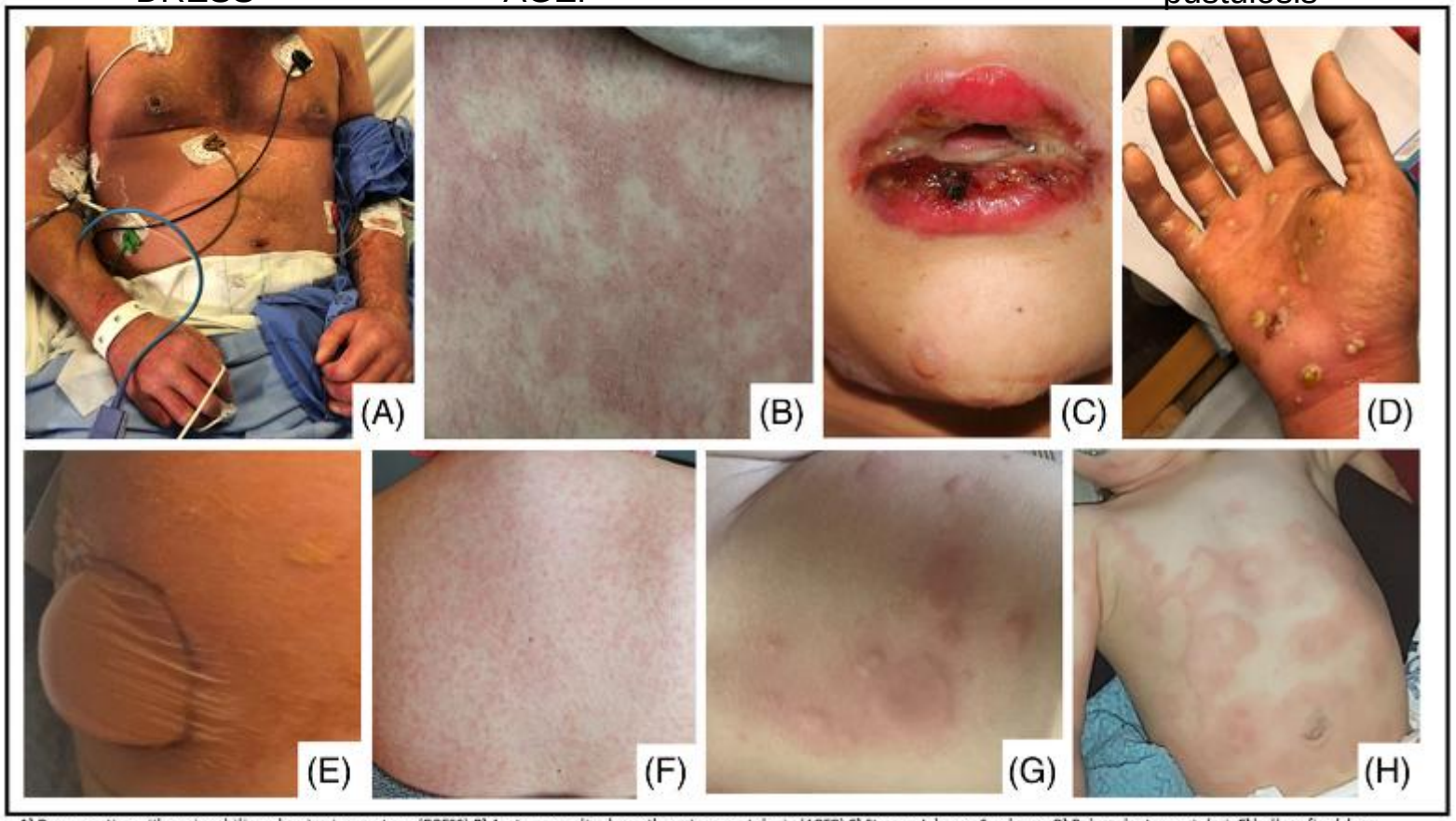
Type B reaction

DRESS

AGEP

SJS

Palmoplantar pustulosis



A) Drug reaction with eosinophilia and systemic symptoms (DRESS) B) Acute generalized exanthematous pustulosis (AGEP) C) Stevens-Johnson Syndrome D) Palmoplantar pustulosis E) bullous fixed drug F) Maculopapular rash G) Urticaria H) Serum sickness like reaction(SSLR)

Bullous fixed drug eruption

Maculopapular rash

Urticaria

Serum sickness like reaction

Br J Clin Pharmacol. 2024;90:1838–1855

Cutaneous adverse drug reactions (CADRs)

- The most frequently reported are maculopapular rash, urticaria/angioedema, fixed drug eruption and erythema multiforme.
- Less common but more severe patterns include erythroderma, drug reaction with eosinophilia and systemic symptoms(DRESS), and Stevens–Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) spectrum.
- Almost any drug can induce a CADR, but antibiotics, nonsteroidal anti-inflammatory drugs and antiepileptics are the most frequently involved.

Br J Clin Pharmacol. 2024;90:1838–1855

Immunologic drug reactions

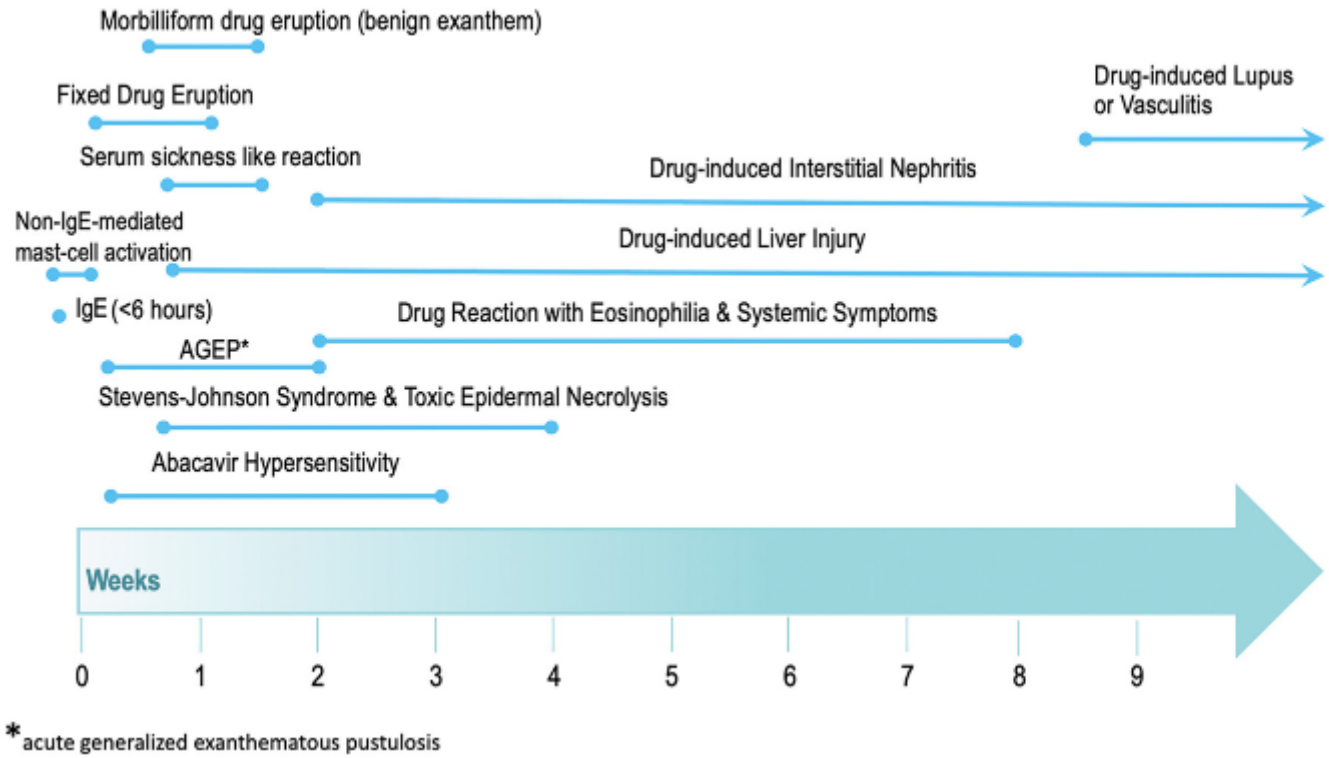
TABLE 45-8

Immunologic Drug Reactions

TYPE OF REACTION	PATHOGENESIS	EXAMPLES OF CAUSATIVE DRUG	CLINICAL PATTERNS
Type I	Immunoglobulin (Ig) E-mediated; immediate-type immunologic reactions	Penicillin, other antibiotics	Urticaria/angioedema of skin/mucosa, edema of other organs, and anaphylactic shock
Type II	Drug + cytotoxic antibodies cause lysis of cells such as platelets or leukocytes	Penicillin, sulfonamides, quinidine, isoniazid	Petechiae resulting from thrombocytopenic purpura, drug-induced pemphigus
Type III	IgG or IgM antibodies formed to drug; immune complexes deposited in small vessels activate complement and recruitment of granulocytes	Immunoglobulins, antibiotics, rituximab, infliximab	Vasculitis, urticaria, serum sickness
Type IV	Cell-mediated immune reaction; sensitized lymphocytes react with drug, liberating cytokines, which trigger cutaneous inflammatory response	Sulfamethoxazole, anti-convulsants, allopurinol	Morbilliform exanthematous reactions, fixed drug eruption, lichenoid eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis

From Wolff K, Johnson R, Saavedra AP, et al. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*. 8th ed. New York, NY: McGraw-Hill; 2017, Table 23-7, with permission.

Time line of drug hypersensitivity reactions



J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.

Cutaneous adverse drug reactions based in morphology

TABLE 1 Cutaneous adverse drug reactions based in morphology

Exanthematous	Urticaria/urticaria-like or flushing	Pustular	Bullous	Miscellaneous
Morbilliform drug eruption	IgE-mediated urticaria	Drug -induced palmoplantar pustulosis	Bullous fixed drug eruption	Drug-induced SLE
SDRIFE	Urticaria multiforme[a]	AGEP	Erythema multiforme[a]	Alopecia
Drug-induced hypersensitivity syndrome/DRESS	Serum sickness-like reaction	ALEP	Drug-induced bullous pemphigoid	Photosensitivity
Drug-induced erythroderma	Serum sickness	Drug-induced subcorneal pustular dermatosis	Drug-induced pemphigus	Vasculitis
Serum sickness	NSAIDs hypersensitivity (urticaria/angioedema)		Drug-induced linear IgA bullous dermatosis	
Contact dermatitis	Red man syndrome		Drug-induced dermatitis herpetiformis	
Leukocytoclastic vasculitis (purpuric)	Infusion reaction		SJS/TEN	
			Bullous DRESS	
			Contact dermatitis	

AGEP, acute generalized exanthematous pustulosis; ALEP, acute localized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; NSAID, nonsteroidal anti-inflammatory drug; SJS/TEN, Stevens–Johnson syndrome and toxic epidermal necrolysis spectrum; SDRIF, symmetric drug-related intertriginous and flexural erythema; SLE, systemic lupus erythematosus.

[a]These conditions are mostly associated with infectious agents.

Br J Clin Pharmacol. 2024;90:1838–1855

Severe cutaneous adverse reactions (SCARs)

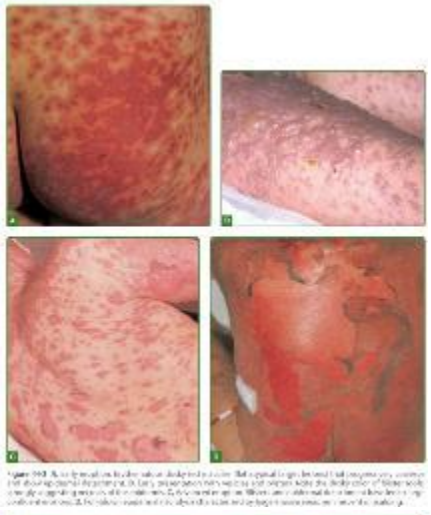
- Severe cutaneous adverse reactions (SCARs) to drugs are associated with morbidity, mortality, health-care costs, and drug development challenges.
- SCARs to drugs cover a broad spectrum of entities mainly consisting of
  - Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
  - Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
  - Acute generalized exanthematous pustulosis (AGEP)
- SCARs are rare, but they have high mortality rates (AGEP: <5%, DRESS: 5%–10%, SJS/TEN: 10%–40%)

Lancet 2017; 390: 1996–2011
Front Pharmacol. 2023 Apr 26;14:1183491.

SJS and TEN

- Rare and **severe cutaneous adverse reactions** (SCARs)
  - characterized by **widespread epidermal necrosis and sloughing of skin and mucosa**
  - disease spectrum classified with the affected TBSA of skin detachment
  - associated with high mortality rate: **SJS: 1~10% and TEN: 20~30%**
- **Clinical manifestations:**

Macular spots, flaccid blisters, epidermal detachment, positive Nikolsky's sign and severe mucosal erosions



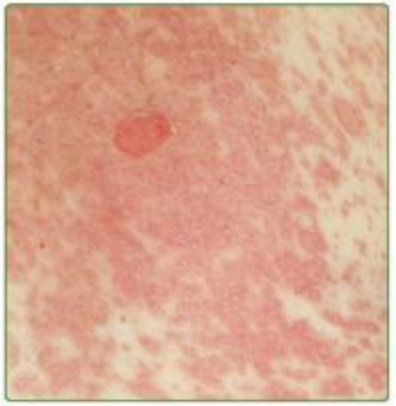
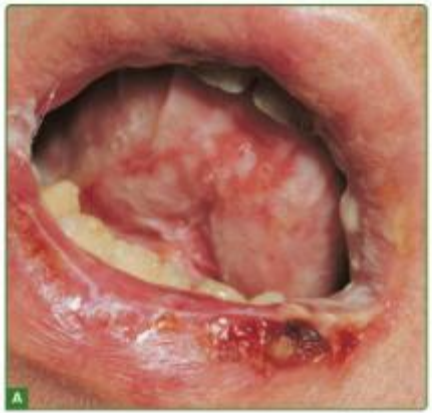


Figure 44-3 Early exanthematous phase with Nikolsky sign.



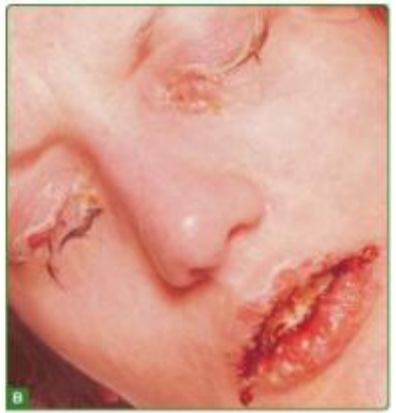


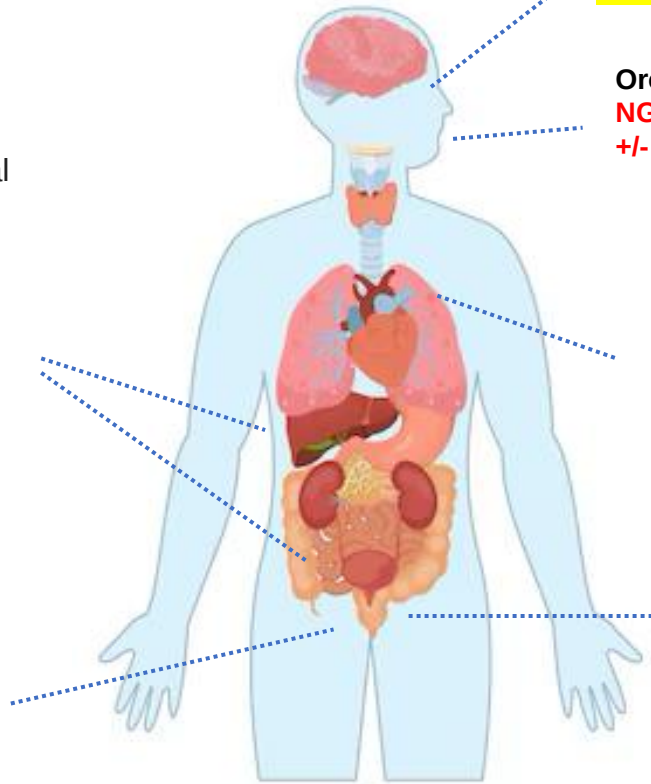
Figure 44-5 **A.** Extensive erosions and necroses of the lower lip and oral mucosa. **B.** Massive erosions covered by crusts on the lips. Note also shedding of the eyelashes.

Fitzpatrick 9th edition

Extracutaneous manifestations of SJS/TEN

Ocular

Gastrointestinal/hepatic
Acute phase: intestinal infarcts and mesenteric ischemia(severe abdominal pain, hematemesis, and diarrhea), **drug-induced liver injury**
Chronic phase(rare): esophageal strictures



Oropharyngeal mucosa
NG insertion
+/- tracheal tube intubation to protect airway

Bronchial epithelium sloughing
Acute phase: pulmonary edema, atelectasis, and bacterial pneumonia-> up to 38% of SJS/TEN patients may require **mechanical ventilation**
Chronic phase(rare): bronchiolitis obliterans, respiratory tract obstruction, bronchiectasis

Genitourinary
Acute phase: Penile erosions, meatal involvement(dysuria and hematuria)
Chronic phase(rare): penile adhesions, urethral strictures, and phimosis

Gynecologic
Acute phase: vaginal erosions and ulcerations, dysuria, urinary retention, and vaginal discharge, pain, and bleeding
Chronic phase(rare): vulvar adhesions and vaginal stenosis

Ther Adv Chronic Dis. 2020;11:2040622319894469.

TABLE 44-2

SCORTEN: A Prognostic Scoring System for Patients with Epidermal Necrolysis

SCORTEN	
PROGNOSTIC FACTORS	**POINTS**
Age > 40 yr	1
Heart rate > 120 beats/min	1
Cancer or hematologic malignancy	1
Body surface area involved >10%	1
Serum urea level > 10 mM	1
Serum bicarbonate level >20 mM	1
Serum glucose level > 14 mM	1
Scorten	**Mortality rate (%)**
0–1	3.2
2	12.1
3	35.8
4	58.3
5	90

Data from Bastuji-Garin S, Fouchard N, Bertocchi M, et al: SCORTEN: A severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol.* 2000;115:149.

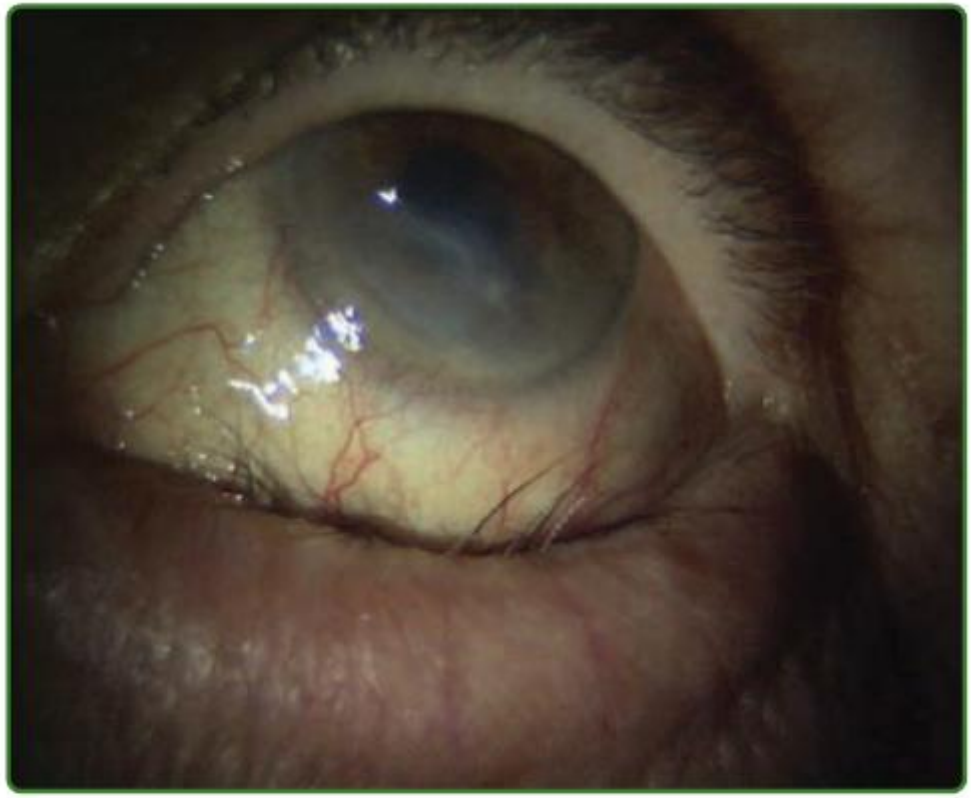


Figure 44-7 Late ocular complications of epidermal necrolysis. Note opaque corneal epithelium, neovessels, and irritating eyelashes on lower eyelids. (Used with permission from Julie Gueudry, MD, and Marc Muraine, MD,

OCULAR MANIFESTATIONS OF SJS/TEN

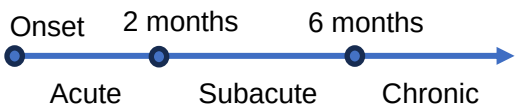
- In the acute stage, **more than 50%** (40-80%) of patients experience ocular complications ranging from minimal (e.g., mild conjunctival hyperemia) to severe (e.g., corneal melting and perforation), out of which **43–89%** progress to chronic ocular complications.

- Ocular sequelae(20-75%) are **the most significant chronic complications of SJS/TEN in survivors:**
  - **Dry eye (17.2%)** was the most frequent ocular sequelae identified within 3 months after hospital discharge followed by **symblepharon (4.7%)** and **corneal scarring (4.7%).**

- **The severity of the acute ocular disease** has been identified as a **significant risk factor for chronic ocular complications.**

Ocul Surf. 2020;18(3):517-522.

Severity correlated significantly with the final visual outcome



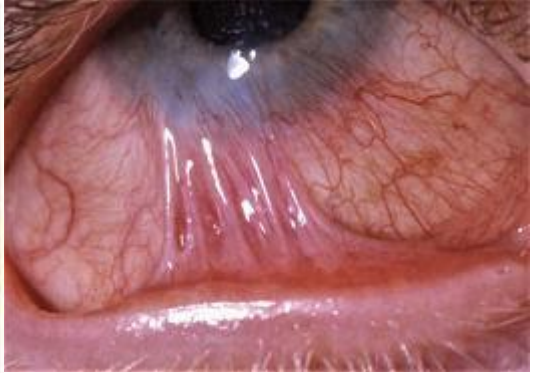
Acute and chronic complications		
Conjuctiva	**Cornea**	**Eyelid**
• **Hyperemia** • **Symblepharon formation**	• **Superficial punctate keratopathy (SPK)** • **Epithelial defect** • **Loss of the palisades of Vogt (POV)** • **Conjunctivalization** • **Neovascularization** • **Opacification** • **Keratinization components**	• **Trichiasis** • **Mucocutaneous junction involvement** • **Meibomian gland involvement** • **Punctal damage**

- Evaluations
  - **Fluorescein** was applied to the eyes and examined the eyes **by the handheld direct ophthalmoscope.**
  - Inspected area including eyelids, fornix, palpebral conjunctiva, bulbar conjunctiva, and cornea
  - daily examination is important in the acute phase due to unpredictable changes

Ocul Surf. 2020;18(3):517-522.
Front Med (Lausanne). 2021;8:670643.

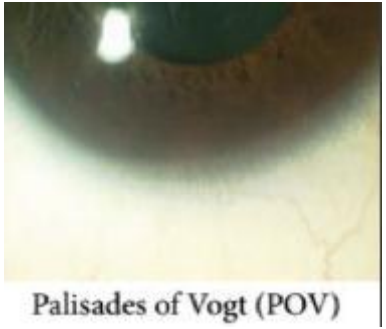
Metcalfe D, Iqbal O, Chodosh J, Bouchard CS, Saeed HN. Acute and Chronic Management of Ocular Disease in Stevens Johnson Syndrome/Toxic Epidermal Necrolysis in the USA. Front Med (Lausanne). 2021;8:662897.

Acute conjunctival hyperemia with no epithelial sloughing



Palpebral conjunctival sloughing-> Symblepharon

Acute corneal epithelial defect (arrow) stained with fluorescein



Loss of the palisades of Vogt

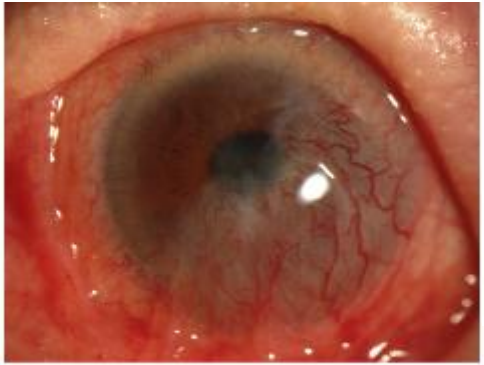
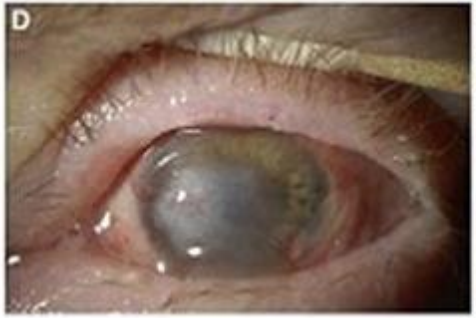


Figure 6. Loss of limbal palisades in patient post SJS/TEN. Note the 360 degrees of limbal vascularization, even where the fibrovascular pannus is absent.

Conjunctivalization, Neovascularization



Chronic dense corneal neovascularization and opacity

Complete ocular surface keratinization in an eye devoid of aqueous tears

Sulfonamide was responsible for one third antibiotic-associated SJS/TEN, whereas the macrolide class was the least common class causing antibiotic-associated SJS/TEN

Antibiotic class	Studies, No.	Proportion (95% CI), %	I^2, %	τ^2	*P* value[a]
Sulfonamides	38	32 (22-44)	91	0.112	<.001
Penicillins	38	22 (17-28)	63	0.019	<.001
Cephalosporins	38	11 (6-17)	77	0.038	<.001
Fluoroquinolones	38	4 (1-7)	69	0.025	<.001
Macrolides	38	2 (1-5)	43	0.009	<.001

JAMA Dermatol. 2023 Feb 15;159(4):384–392

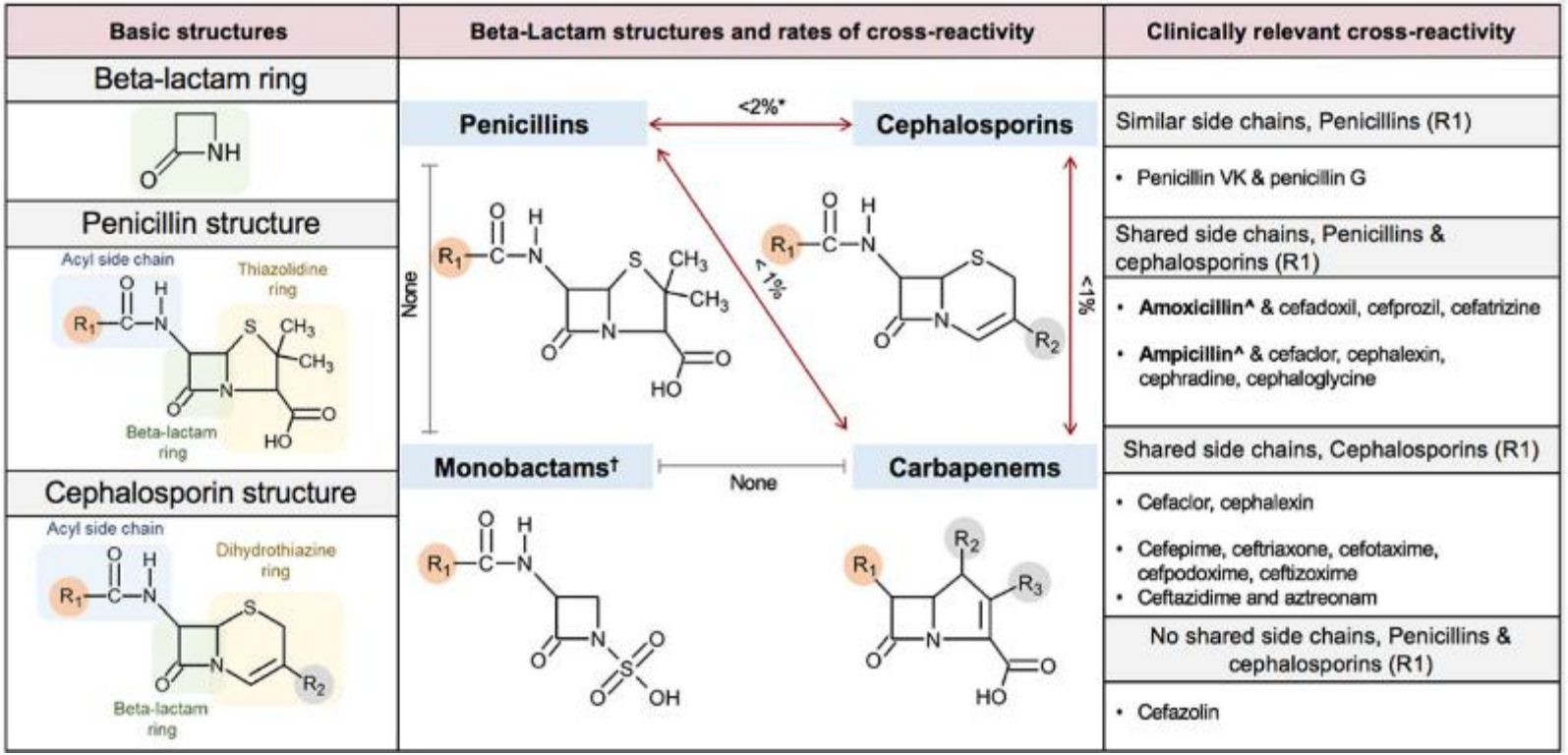
Absolute risks of serious cutaneous adverse drug reactions (cADRs) following oral antibiotic therapy

Table 2. Crude Rate of Serious cADRs Within 60 Days of Antibiotic Prescription[a]

Antibiotic class	No. of exposures	No. of serious cADRs	Events per 1000 exposures (95% CI)
Cephalosporins	5 076 176	24 997	4.92 (4.86-4.99)
Sulfonamides	2 730 810	8780	3.22 (3.15-3.28)
Fluoroquinolones	6 825 283	16 939	2.48 (2.44-2.52)
Nitrofurantoin	3 627 644	8464	2.33 (2.28-2.38)
Penicillins	8 666 828	16 822	1.94 (1.91-1.97)
Macrolides	4 709 840	8483	1.80 (1.76-1.84)
Other antibiotics[b]	2 477 673	9786	3.95 (3.87-4.03)
All antibiotics	34 114 254	72 449	2.12 (2.11-2.14)

JAMA.2024;332(9):730-737.

β-Lactam structure and cross-reactivity β-Lactam antibiotics include penicillins, cephalosporins, carbapenems, and monobactams



Lancet. 2019 January 12; 393(10167): 183–198.

臨床常見的磺胺類藥物

藥品種類	藥物名稱	
抗生素	Sulfamethoxazole (Baktar/ Co-trimoxazole)	常用；常過敏
免疫調節劑	Dapsone (抗痲瘋病)	少用；常過敏
免疫調節劑	Sulfasalazine	少用；常過敏
抗癲癇	Zonisamide	少用；常過敏

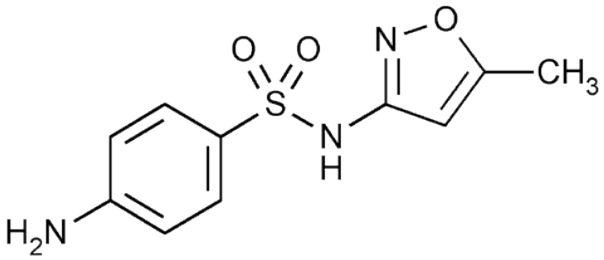
藥品種類	藥物名稱	
利尿劑	Bumetanide Furosemide Indapamide	常用；少過敏
降血糖藥	Glyburide Glimepride Gliclazide	常用；少過敏
碳酸酐酶抑制劑	Acetazolamide Dorzolamide	常用；少過敏
止痛消炎	Celecoxib	常用；少過敏
其他	Topiramate Sumatriptan Sotalol	少用；少過敏

撲菌特錠 (Baktar)(Co-trimoxazole) 抗生素

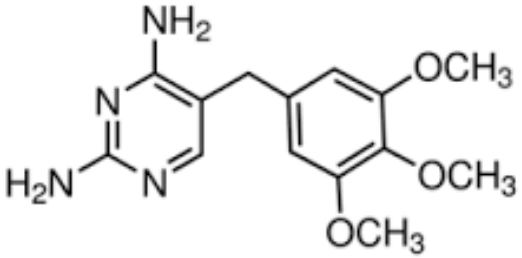
- 撲菌特錠抗生素是全球廣泛使用 半世紀的老藥
- 廣泛使用於皮膚感染、上下呼吸道感染、腎臟尿路感染、腸胃道感染、生殖器感染等等
- 適應症：葡萄狀球菌、鏈鎖球菌、肺炎雙球菌、大腸菌、赤痢菌及綠膿菌引起之感染症
- 撲菌特錠抗生素有其不可取代的地位。

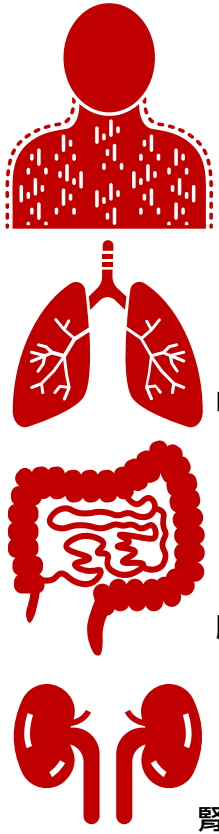
Baktar (Sulfamethoxazole 400mg + Trimethoprim 80mg)

Sulfamethoxazole

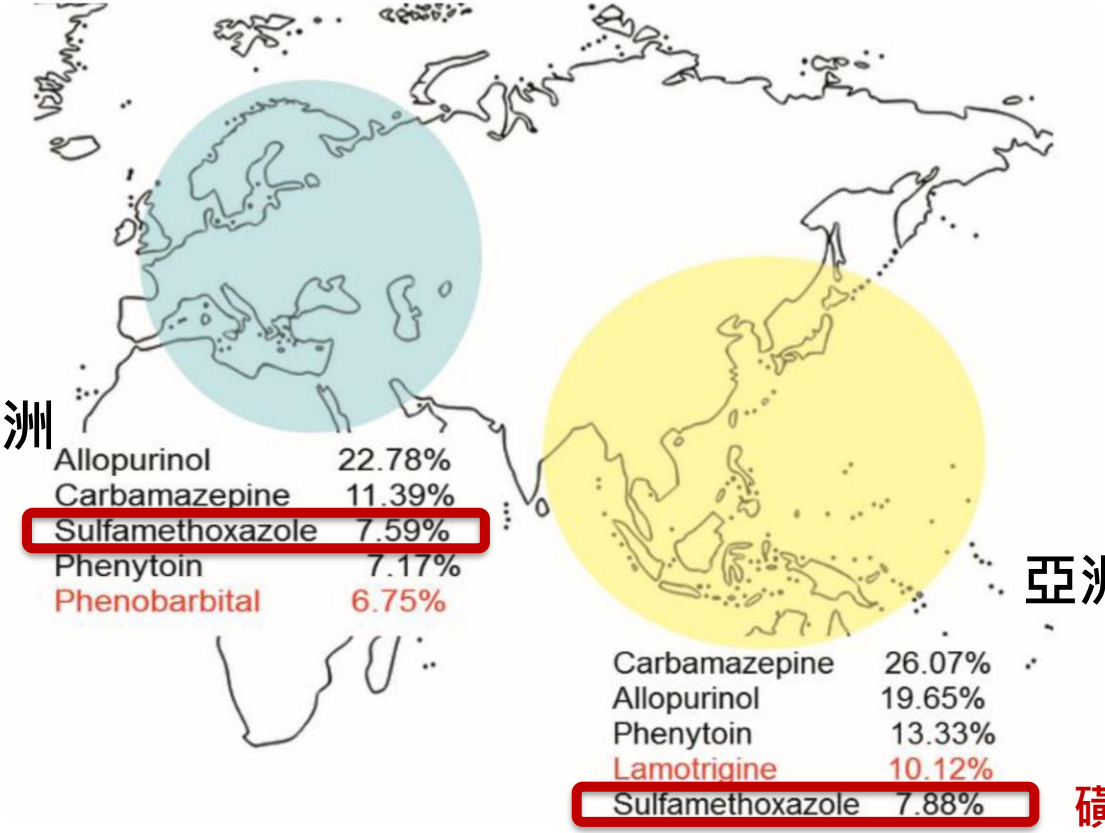


Trimethoprim





亞洲人與歐洲人種中最常見的引起嚴重藥物過敏的藥物



Clin Pharmacol Ther. 2019 Jan;105(1):112-120.

TABLE II. Drugs to avoid in patients with a history of a sulfonamide antimicrobial adverse reaction

Drug or compound	Comments
Sulfonamide antimicrobials	
• Sulfamethoxazole (oral/parenteral: cotrimoxazole, *Septra*)	Avoid all sulfonamide antimicrobials.
• Sulfasalazine (oral: *Salazopyrin*)	• Sulfasalazine should be avoided, as it is metabolized to sulfapyridine (a sulfonamide antimicrobial) and 5-ASA
• Sodium sulfacetamide (ophthalmic)	
• Silver sulfadiazine (topical: *Flamazine*)	
Other drugs	
• Dapsone (oral and topical)	• Conflicting information on cross-reactivity between dapsone and sulfonamide antimicrobials; suggest avoidance especially in patients with severe reactions.[19]
• Darunavir (oral: *Prezista*, *Prezcobix*)	• Fosamprenavir is a derivative of sulfanilamide and caution is recommended in patients with a history of sulfonamide antimicrobial allergy.
• Fosamprenavir (oral: *Telzir*)	• Although reports suggest that many patients with a sulfonamide allergy may tolerate darunavir, caution is advised when initiating therapy with darunavir[18]
Trimethoprim (oral)	• Trimethoprim should be avoided in patients who reacted to sulfamethoxazole-trimethoprim, as it is unknown which component was the causative agent

ASA, 5-Aminosalicylic acid.

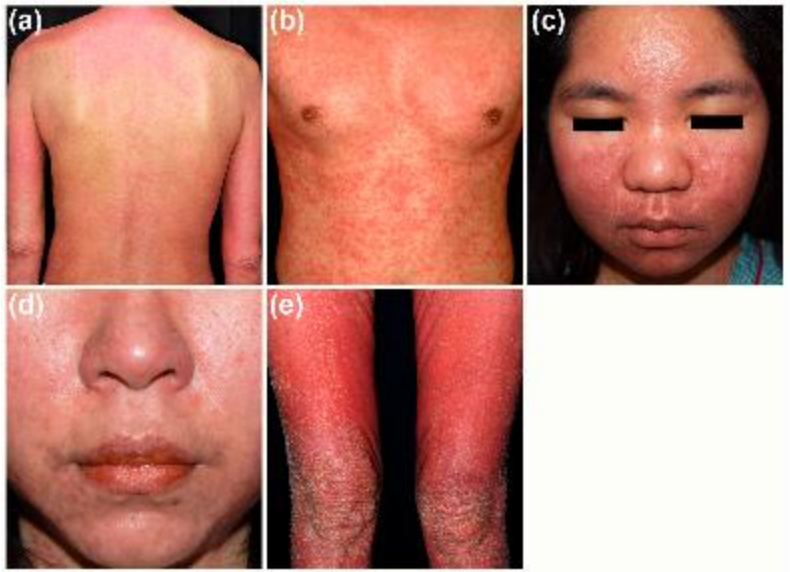
J Allergy Clin Immunol Pract. 2019 Sep-Oct;7(7):2116-2123

SJS/TEN 六大早期症狀圖

藥害基金會

DRESS

- DRESS is a rare but severe cutaneous and systemic drug-delayed hypersensitivity reaction, mediated by T cell activation.
- It is a life-threatening disease with cutaneous presentation and internal organ involvement, and its mortality rate is about 5-10%. The incidence of DRESS is still unclear, with an estimated overall population risk of between 1 in 1000 and 1 in 10,000 drug exposures.
- Drugs, drug's metabolites and/or coincidental viral infection such as human herpesvirus (HHV)-6 and 7, cytomegalovirus (CMV) and Epstein-Barr virus (EBV)-induced T cell activation seem to play an important role in the pathogenesis of DRESS.



Front Pharmacol. 2023 Apr 26;14:1183491.
Int. J. Mol. Sci. **2017**, 18, 1243

Table 1. The common culprit drugs in drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

Category	Drugs
Anti-convulsants	Carbamazepine [2,11,14,18], lamotrigine [2,11,14,18], phenobarbital [11,14,18], phenytoin [2,11,14,18], oxcarbazepine [11,14], gabapentin [37]
Anti-bacterial	Amoxicillin [11,14], ampicillin [14,18], azithromycin [38], levofloxacin [39], minocycline [11,14,18], piperacillin/tazobactam [40], vancomycin [11,14,18]
Anti-tuberculosis	Ethambutol [18,41], isoniazid [2,18,41], pyrazinamide [18,41], rifampin [18,41], streptomycin [11,18,41]
Anti-retroviral agents	Abacavir [11,18], nevirapine [11,14,18]
Anti-hepatitis C virus agents	Boceprevir [42,43], telaprevir [42,44]
Anti-pyretic/analgesics	Acetaminophen [45], diclofenac [2], celecoxib [11,18], ibuprofen [11,18]
Sulfonamides	Dapsone [2,11,14,18], sulfamethoxazole-trimethoprim [2,11,14,18], sulfasalazine [2,11,14,18]
Targeted therapeutic agents	Dorafenib [46], vismodegib [47], vemurafenib [48]
Others	Allopurinol [2,11,14,18], chinese herbal medicine [2], imatinib [11], mexiletine [11,18], omeprazole [11], strontium ranelate [11]

Bold characters highlight the most frequently reported culprit drugs in the literature, which are with a frequency of more than 10 cases ever reported.

Int. J. Mol. Sci. **2017**, 18, 1243;

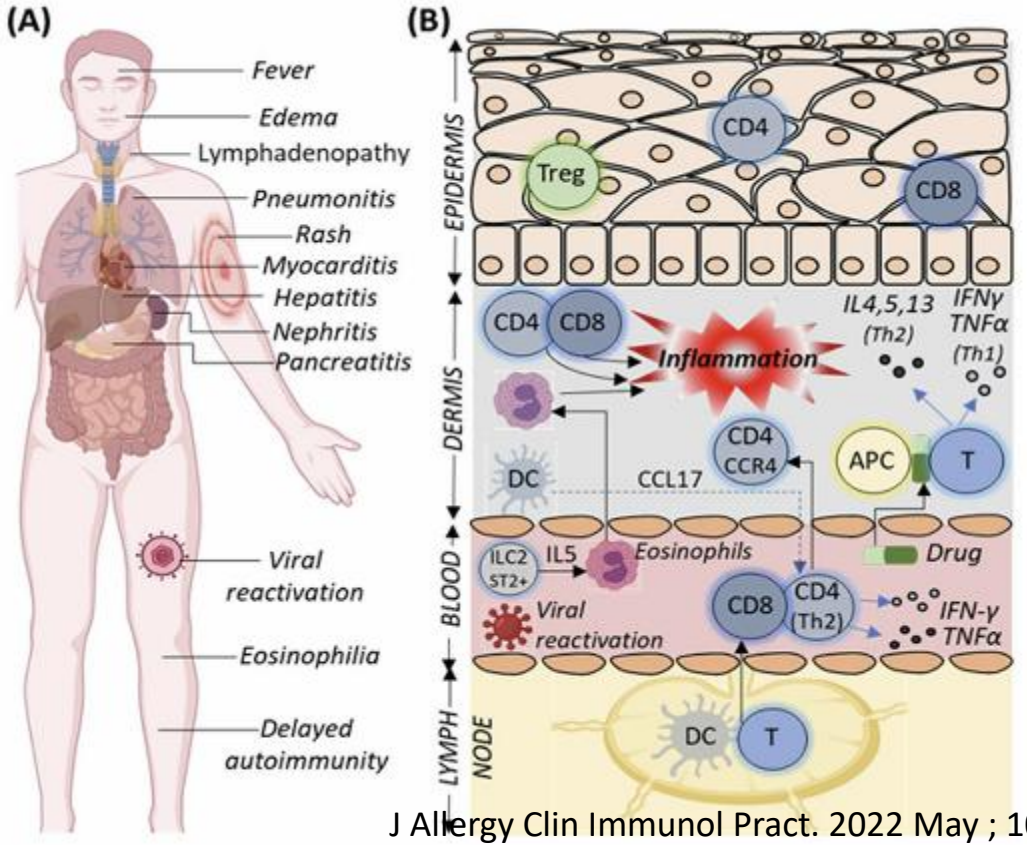
Table 2. The RegiSCAR scoring system for diagnosing DRESS syndrome.

Items	Score			Comments
	−1	0	1	
Fever ≧ 38.5 °C	N/U	Y		
Enlarged lymph nodes		N/U	Y	>1 cm and ≧ 2 different areas
Eosinophilia ≧ 0.7×10^9/L or ≧ 10% if WBC < 4.0×10^9/L		N/U	Y	Score 2, when ≧ 1.5×10^9/L or ≧ 20% if WBC < 4.0×10^9/L
Atypical lymphocytosis		N/U	Y	
Skin rash				Rash suggesting DRESS: ≧ 2 symptoms: purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation
Extent > 50% of BSA		N/U	Y	
Rash suggesting DRESS	N	U	Y	
Skin biopsy suggesting DRESS	N	Y/U		
Organ involvement		N	Y	Score 1 for each organ involvement, maximal score: 2
Rash resolution ≧ 15 days	N/U	Y		
Excluding other causes		N/U	Y	Score 1 if 3 tests of the following tests were performed and all were negative: HAV, HBV, HCV, Mycoplasma, Chlamydia, ANA, blood culture

ANA: anti-nuclear antibody; BSA: body surface area; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; N: no; U: unknown; WBC: white blood cell; Y: yes.

Int. J. Mol. Sci. **2017**, 18, 1243;

Immunopathogenesis of DRESS



J Allergy Clin Immunol Pract. 2022 May ; 10(5): 1155–1167

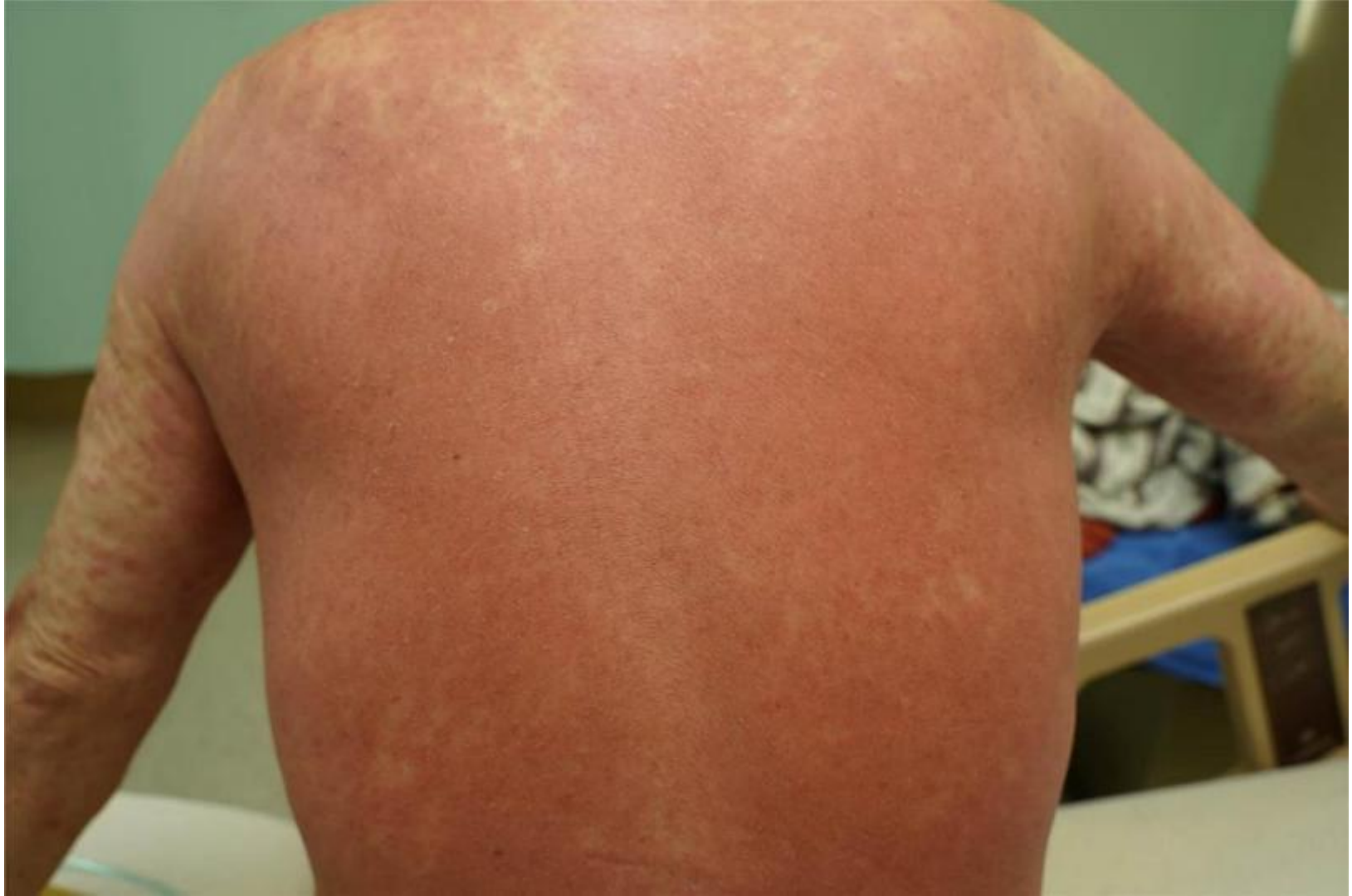
Acute generalized exanthematous pustulosis

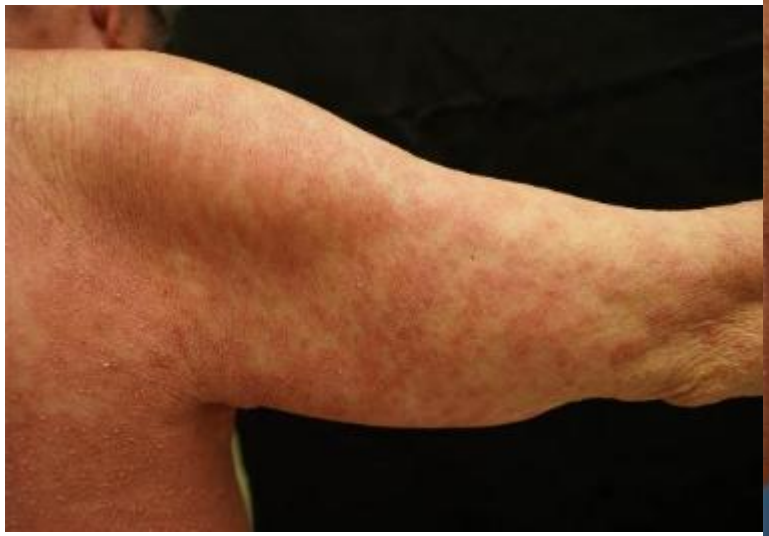
- Acute generalized exanthematous pustulosis (AGEP) is a severe, usually drug-related reaction, characterized by an acute onset of mainly small non-follicular pustules on an erythematous base and spontaneous resolution usually within two weeks. Systemic involvement occurs in about 20%ofcases.
- The course is mostly benign, and only in rare cases complications lead to life-threatening situations.
- 90% of cases are associated withdrugs:
  - Aminopenicillins, pristinamycin, sulphonamides, quinolones, hydroxychloroquine, terbinafin and diltiazem are the most frequent causative drugs.
  - In particular cases, AGEP is induced by bacterial, viral or parasitic infections (e.g., parvovirus B19 , mycoplasma, cytomegalovirus, coxsackie B4, Chlamydia pneumoniae.

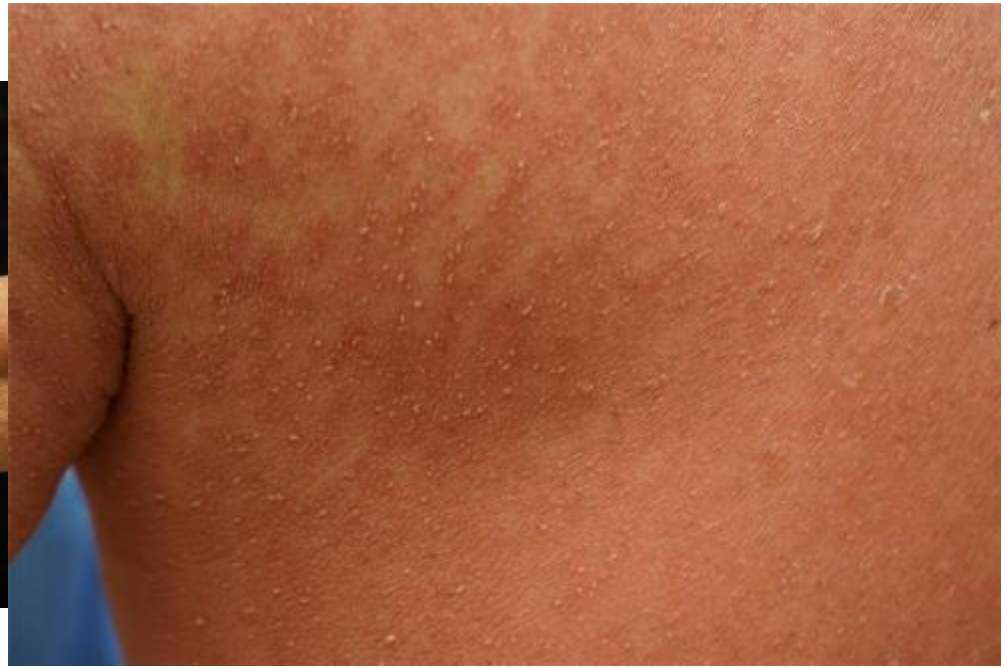
Int. J. Mol. Sci. 2016, 17, 1214;

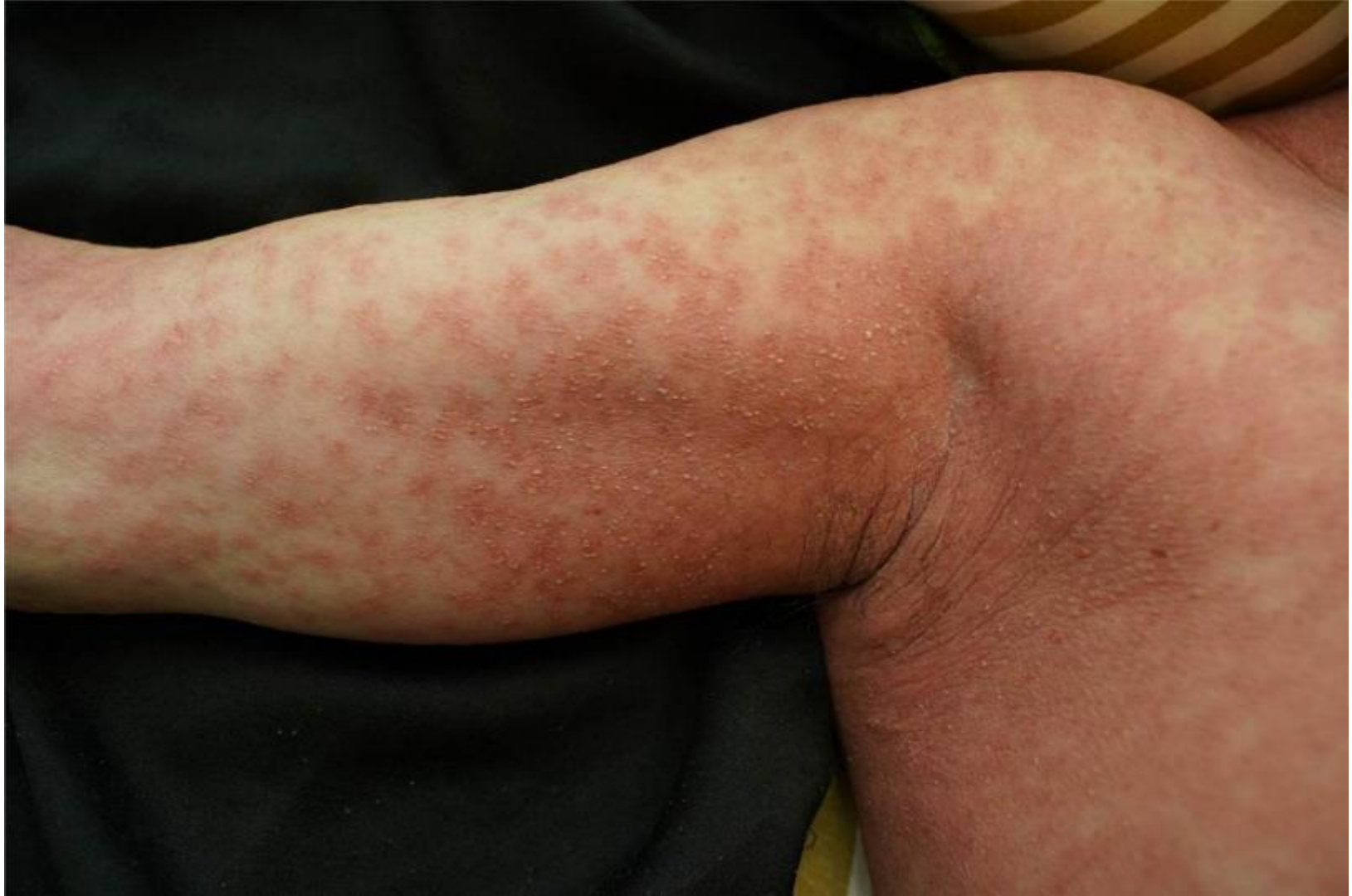
Case

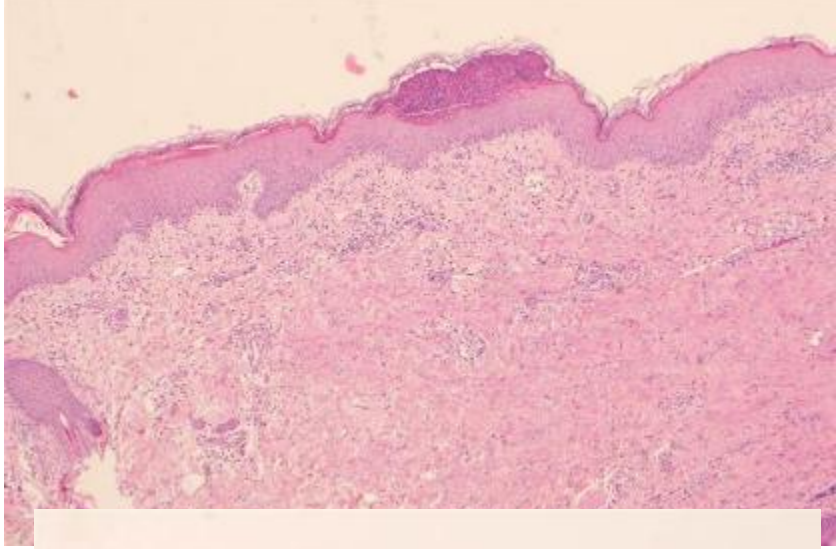
- 50+ y/o male
- Deny underlying disease
- Fever and generalized painful erythematous plaques with pustules
- Visit ER
- Lamisil for onychomycosis 2 days ago

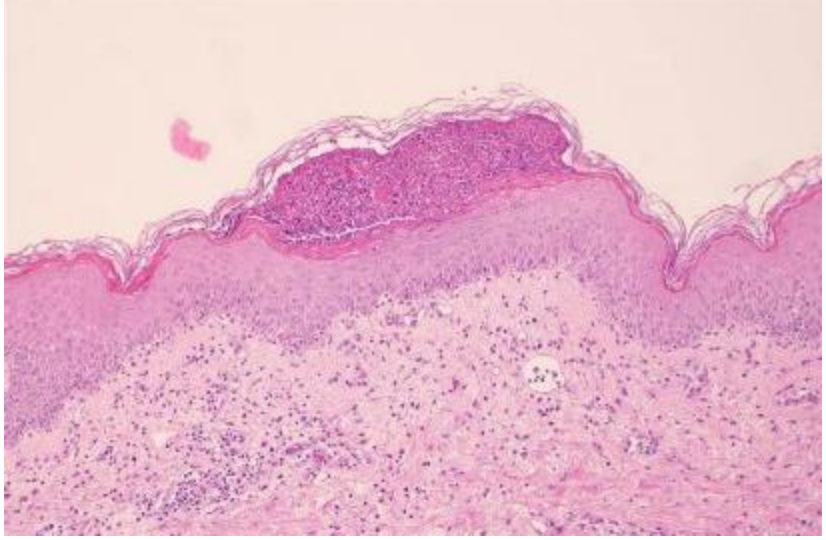


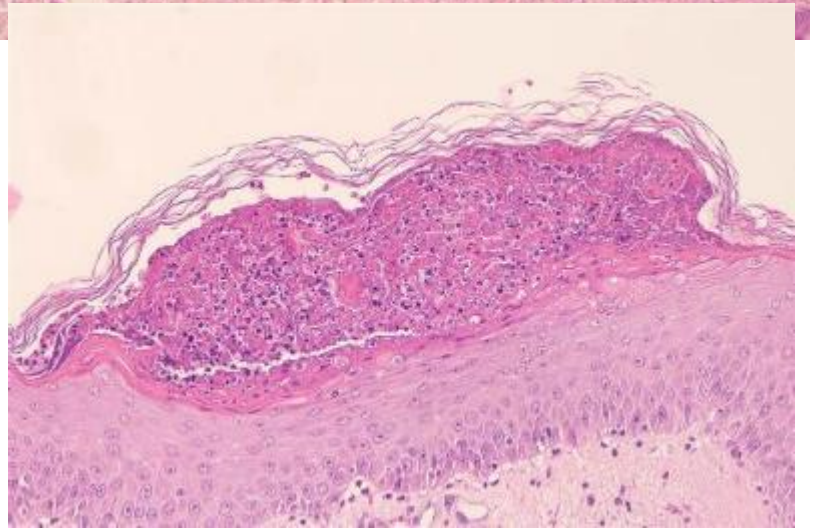


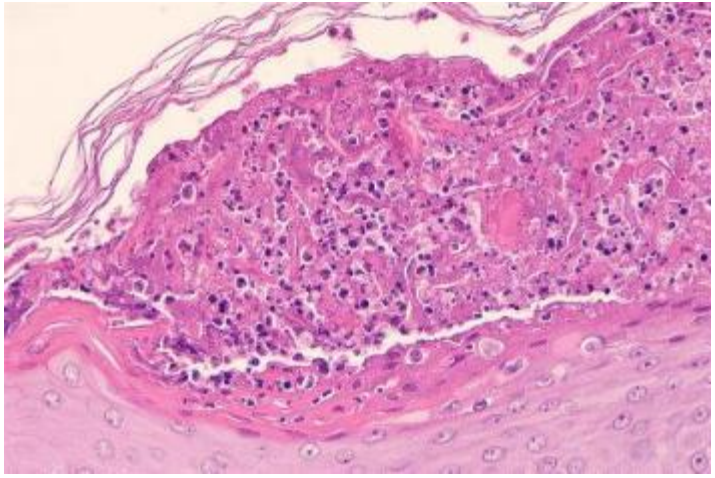




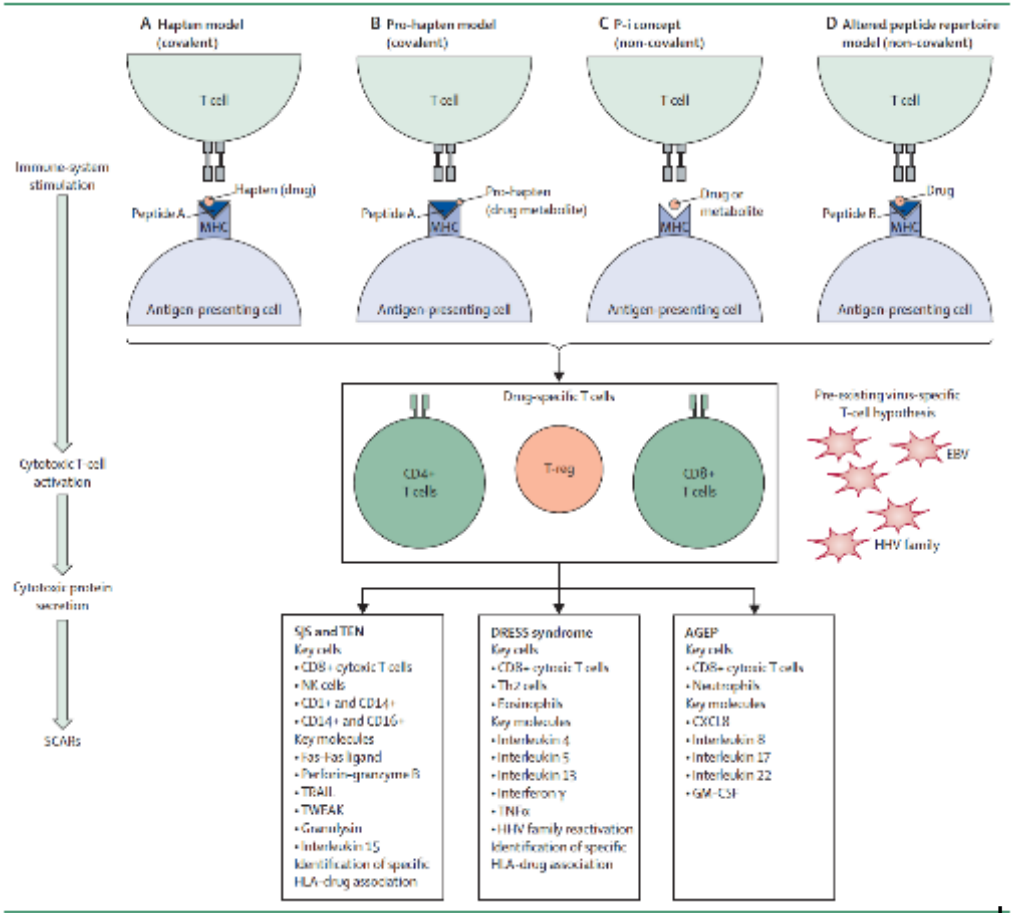






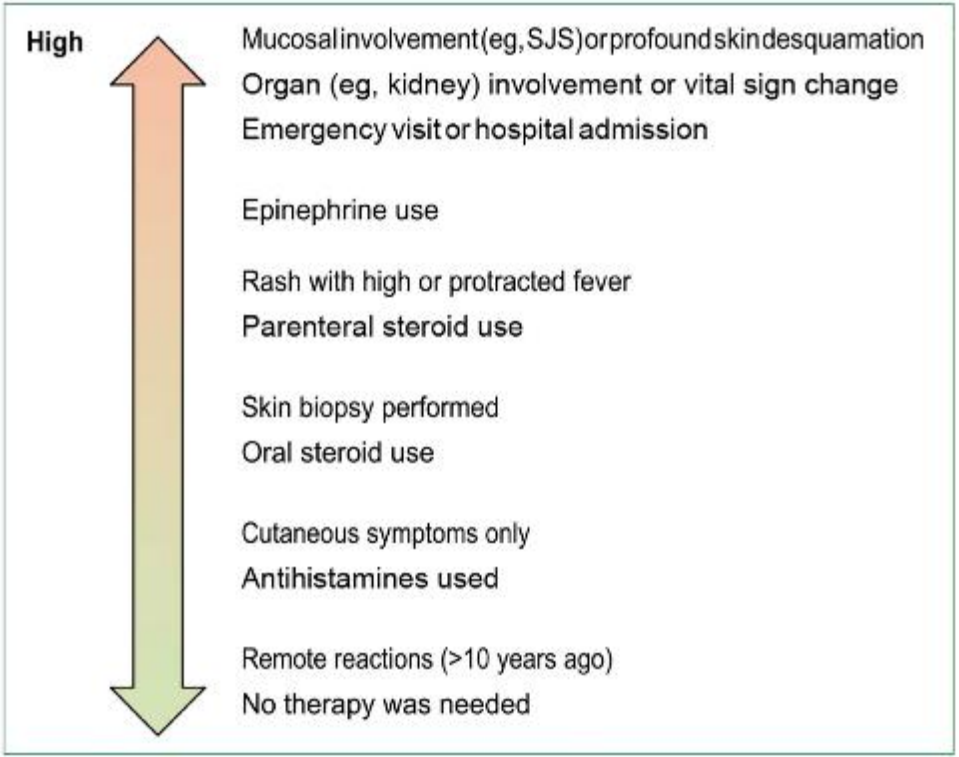


Pathogenesis of SJS/TEN/DRESS



Lancet 2017; 390: 1996–2011

Patient-reported historical details can be used to distinguish patients at high and low risk



Lancet. 2019 January 12; 393(10167): 183–198.

Diagnosis algorithm for SCARs

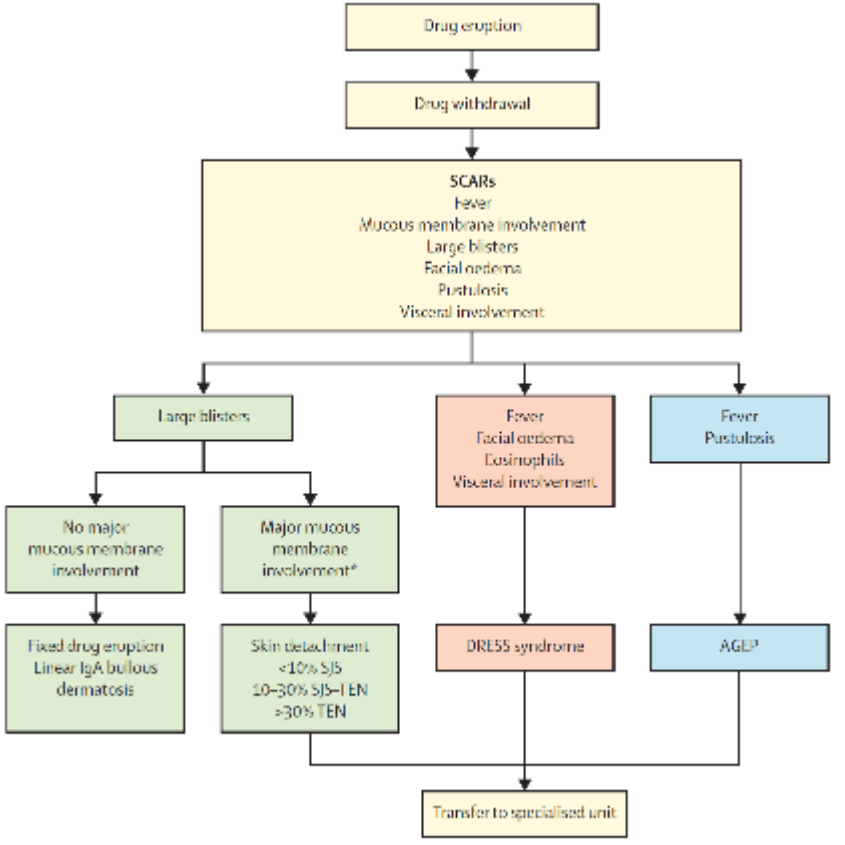


Figure 2: Decisional algorithm for SCARs

Genetic associations with SCARs in different populations

Causative drug	Genetic associations	SCAR	Ethnicity	Reference	Clinical implementations and recommendations
Antiepileptic drug					
Carbamazepine	B*15:02	SJS/TEN	Han Chinese	[19, 25]	1. Labeled by Taiwan FDA, Hong Kong Department of Health, Singapore Ministry of Health, Thailand HITAP, India MOHFW, US FDA, Canada HCSC, PMA. 2. National health insurance subsidized in Taiwan, China, Hong Kong, Singapore, and Thailand.
			Southeast Asian	[19, 20]	
	B*15:11	SJS/TEN	Northeast Asian	[27, 28]	
			Southeast Asian	[28]	
	B*15:21	SJS/TEN	Southeast Asian	[29]	
	B*54:01	SJS/TEN	Caucasians	[30]	
	A*31:01	DRESS	Han Chinese	[31]	1. Labeled by US FDA, Canada HCSC, Japan, and Taiwan.
			Caucasians	[31, 32]	
		SCARs	Japanese	[33]	
Oxcarbazepine	B*15:02	SJS/TEN	Han Chinese	[23, 25]	1. Labeled by US FDA, EMA and Taiwan FDA. 2. Ongoing clinical trial in Taiwan and China.
Lamotrigine	B*15:02	SJS/TEN	Han Chinese	[25]	Ongoing clinical trial in Taiwan and China.
	B*38	SJS/TEN	Caucasians	[34]	
Phenytoin	B*15:02	SCARs	Han Chinese	[22, 25, 35]	1. Labeled by Canada HCSC, US FDA, and Taiwan FDA. 2. Ongoing clinical trial in Taiwan and China.
			Southeast Asian	[24, 25]	
	B*13:01	SCARs	Asian	[35]	Ongoing clinical trial in Taiwan and China.
	B*15:13	SJS/TEN	Japanese	[36]	Ongoing clinical trial in Taiwan and China.
	B*51:01	SCARs	Han Chinese	[37]	
	CYP2C9*3	SCARs	Asian	[35]	Ongoing clinical trial in Taiwan and China
Phenobarbital	B*51:01	SJS/TEN	Japanese	[36]	
	A*02:07	SJS/TEN	Japanese	[38]	
Zonisamide	A*02:07	SJS/TEN	Japanese	[38]	
Antiinfection drugs					
Antibiotics					
Co-trimoxazole	B*13:01	SCARs	Han Chinese Southeast Asian	[17]	
Piperacillin/tazobactam	B*82	DRESS	Caucasians	[39]	
Sulfamethoxazole	B*38	SJS/TEN	Caucasians	[34]	
Vancomycin	A*32:01	DRESS	Caucasians	[39]	

Front Med (Lausanne). 2021 Jul 15;8:652091

TABLE 3 Drug hypersensitivity testing for cutaneous adverse drug reactions

Drug-induced skin disease type		In vivo testing	In vitro testing	Additional testing
Immediate reaction				
IgE mediated (Urticaria, angioedema, anaphylaxis)		Skin test (prick test) Oral challenge[a]	BAT (not widely available) RAST/ImmunoCAP	Tryptase
Non-IgE mediated urticaria and angioedema (NSAIDs hypersensitivity)		Oral challenge[a]	Not available	Not available
Delayed reaction				
Type II hypersensitivity reaction (drug-induced bullous pemphigus/pemphigoid)		Oral challenge[a]	Not available	Skin biopsy (H&E, immunofluorescence) Serum (indirect immunofluorescence)
Type III hypersensitivity reaction (serum sickness reaction)		No recommended	LTA (not widely available)	Skin biopsy
Type IV hypersensitivity reaction	• Maculopapular rash	Oral challenge[a] IDT	LTA, LTT (not widely available)	Skin biopsy
	• Contact dermatitis	Patch test	Not available	Skin biopsy
	• DRESS	IDT	LTA, LTT, ELISpot (not widely available)	Skin biopsy
	• AGEP	Patch test IDT	LTA, LTT, ELISpot (not widely available)	Skin biopsy
	• SJS/TEN	Not recommended	LTA, LTT, ELISpot (not widely available)	Skin biopsy

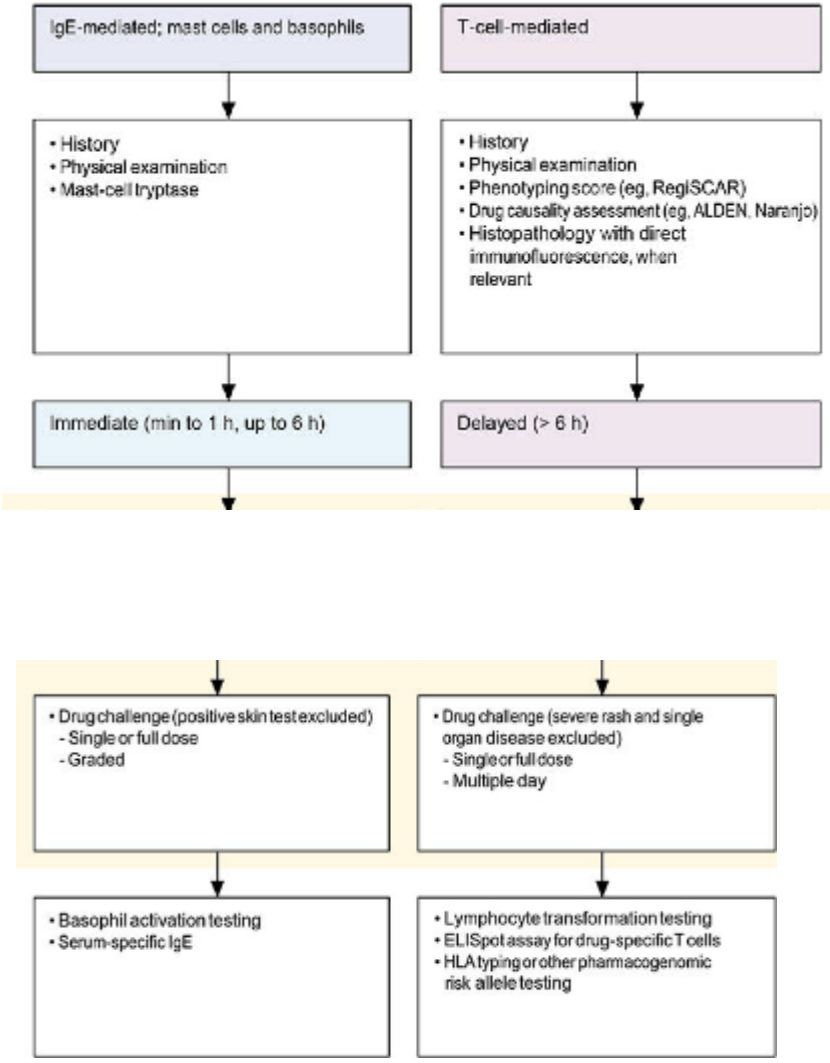
AGEP, acute generalized exanthematous pustulosis; BAT, basophil activation testing; DRESS, drug reaction with eosinophilia and systemic symptoms; ELISpot, enzyme-linked ImmunoSpot; H&E, hematoxylin and eosine; IDT, intradermal testing; IgE, immunoglobulin E; LTA, lymphocyte toxicity assay; LTT, lymphocyte transformation test; NSAID, nonsteroidal anti-inflammatory drug; RAST, radioallergosorbent test.

[a]Not indicated when there is history of severe reaction or anaphylaxis.

Br J Clin Pharmacol. 2024;90:1838–1855

台灣常見藥害救濟過敏藥物基因之發現

排名	藥物名稱	相關基因	發現研究團隊
1	Allopurinol 降尿酸藥物	HLA-B*58:01	長庚醫院 & 中研院
2	Phenytoin 抗癲癇藥物	HLA-B*15:02 CYP2C9	長庚醫院
3	Carbamazepine 抗癲癇藥物	HLA-B*15:02	長庚醫院 & 中研院
6	Co-trimoxazole 磺胺藥抗生素	HLA-B*13:01	長庚醫院



Lancet. 2019 January 12; 393(10167): 183–198.

TABLE 2 Example of diagnostic scoring algorithms and drug causality tools for CADRs

Disease likelihood	**1.- AGEP validation score (EuroSCAR group)** Based on clinical. Laboratory and histological features • Score −10 to 0: No AGEP; score 1–4: Probable; score 5–7: Definite **2.- RegiSCAR score (DRESS)** Based on clinical, laboratory and histological features • Score < 2: No case; score 2–3: Possible; score 4–5: Probable; score > 5: Definite **3.- J-SCAR (DRESS)** Bases on clinical and laboratory features enlisted from 1 to 7 • The diagnosis is confirmed by the presence of all 7 criteria (typical) or from 1–5 (atypical)
Drug causality	**1.- Naranjo score** The ADR probability scale consists of 10 questions. Different point values (−1, 0, +1 or +2) are assigned to each answer (from −4 to 13) • Score 9 or higher: definite; score 5–8: probable; score 1–4: possible if 1–4; ≤0: doubtful **2.- Liverpool causality assessment tool** Flow diagram conformed by sequential questions designed to determine the likelihood of drug causality **3. ALDEN score (SJS/TEN)** Based on 6 parameters, score range from −12 to 10. Score <0: very unlikely; score 0–1: unlikely; score 2–3: possible; score 4–5: probable; score ≥6: Very probable

AGEP, acute generalized exanthematous pustulosis; DRESS, Drug reaction with eosinophilia and systemic symptoms; J-SCAR, Japanese Consensus Group; RegiSCAR, European registry of severe cutaneous adverse reactions.

Br J Clin Pharmacol. 2024;90:1838–1855

TABLE 44-6

Therapeutic Options in the Management of Epidermal Necrolysis[a]

1. Early recognition and immediate withdrawal of offending drugs(s)
2. Supportive treatment
   - Fluid replacement (preferably with a peripheral line)
   - Correct electrolyte imbalance
   - Early nutritional support (nasogastric tube)
   - Culture for skin, blood, and urine specimens
     - (Antibiotics only if bacterial infections are suspected)
     - Prophylactic anticoagulation
3. Skin care
   - Extensive debridement not recommended
4. Early ophthalmologic evaluation and care.
   - Use of preservative-free emollients, antiseptic eye drops, vitamin A

Mechanical disruption of early synechiae

5. Antifungal or antiseptic mouth rinse
6. Systemic steroids
   - Use is controversial

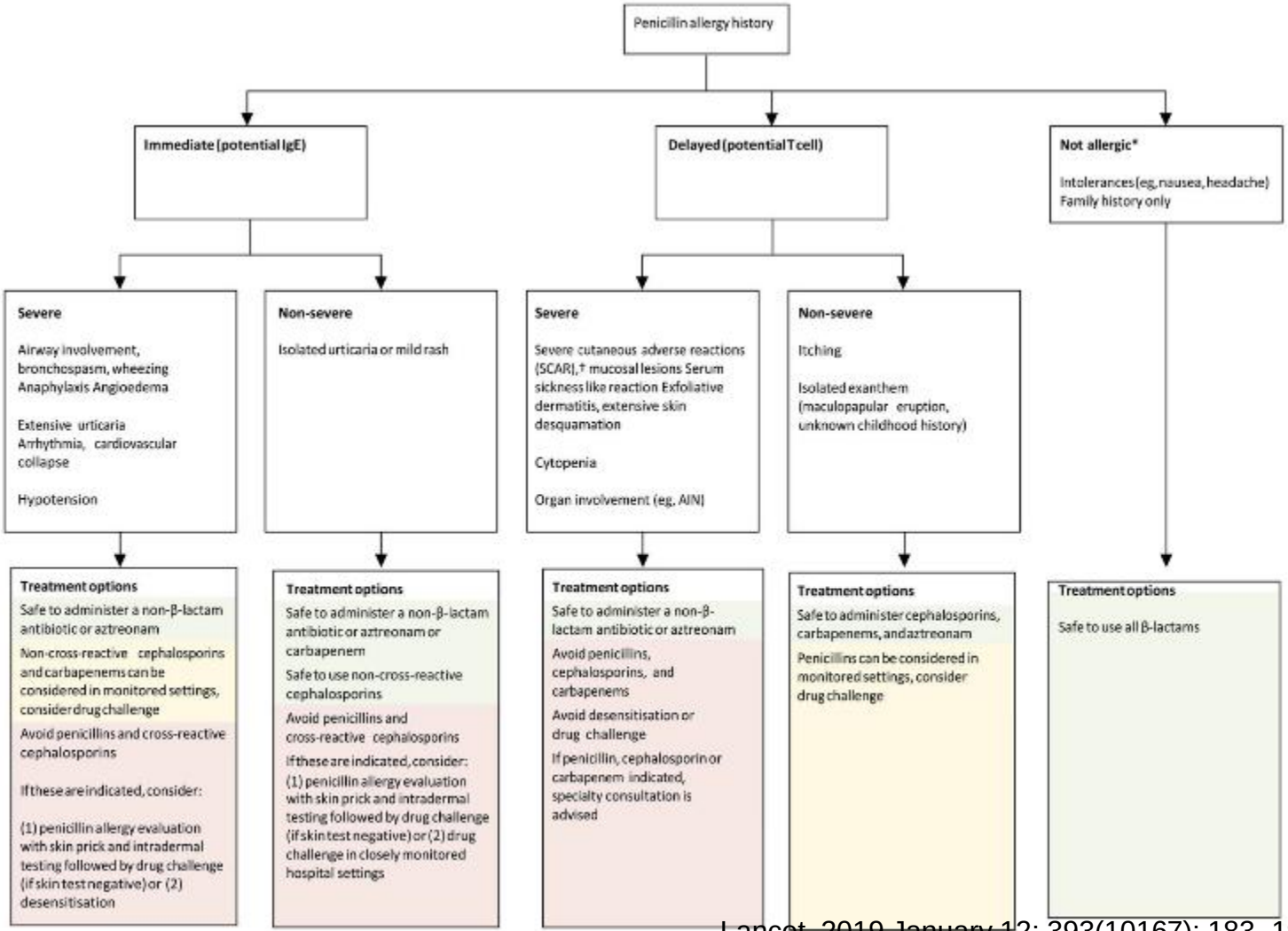
Medium doses for short periods (days rather than weeks) may be beneficial

7. Cyclosporine A
   - Early administration may halt the progression of skin detachment and increase survival
   - Dose: 3 mg/kg for 10 days
8. Anti-TNF monoclonal antibodies
   - Etanercept may be of benefit
   - Extreme caution is advised

Figure 4b: Multidisciplinary approach to management of recovery SJS/TEN (Level V Evidence)

	Early Recovery (<6 months)	Late Recovery (6-12 months)	Lifelong
General Care	• Connect with SJS Foundation • MedicAlert Bracelet	• Address ongoing patient needs and concerns as they arise	
Dermatology	• General skin care including emollients for previously involved skin	• Scar care and revision as needed • Treat mottling or dyspigmentation in cosmetically-sensitive areas	
Ophthalmology	• Continue topical steroids for several months with slow taper • Monitor intraocular pressure frequently • Tailor interventions to individual case	• Regular, lifelong follow-up is required for SJS/TEN survivors	
Gynecology Urology	• Follow-up exam within 3 months • If vaginal mucosa involved, continue dilator daily for 2 weeks and then at least twice weekly for 2-3 months • Switch to estrogen cream for vaginal mucosa for use with the dilator • Calcineurin inhibitor for ongoing inflammation of penile skin	• Ongoing follow-up for urological, gynecologic, and/or obstetric complications	
Psychiatry	• Evaluate for psychological sequelae of SJS/TEN including depression, anxiety, post-traumatic stress disorder and fear of taking medications • Offer individual and group support resources		
Other	• Respirology: Consider pulmonary function testing as a baseline within the first 6 months after discharge for those with lung involvement. Ongoing pulmonary rehabilitation may be required depending on severity of involvement. • Gastroenterology: Follow-up dictated by gastrointestinal involvement (e.g., esophageal stricture, GERD, resolved GI bleed)		
Future	• Consider *ex vivo* (peripheral blood ELIspot, flow cytometry) and *in vivo* (patch testing) drug causality assessments • Genetic testing for known risk alleles in patient and family • Expert guidance on safe medications for patient and family		

J Allergy Clin Immunol Pract. 2018 ; 6(1): 38–69.



Lancet. 2019 January 12; 393(10167): 183–198.

	Treatment		Acute-stage mortality	Outcome	Sequelae	Management after resolution
	Specific	Symptomatic				
SJS and TEN	Drug withdrawal, no RCT-validated curative treatment*	Supportive care strongly recommended, cutaneous and mucous membrane care, enteral feeding, fluid-loss treatment, analgesia, no systematic intubation, environmental temperature ≥28°C, anxiolytics	10–40%	Bacterial superinfection, visceral-specific involvement, lung failure	Dystrophic scars, hyperpigmentation, alopecia, nail loss, visual loss, synechiae, dry eye, symblepharon, dental agenesia, sialadenitis, tooth decay, genital synechiae, psychiatric disorders	Patch testing at month 6; follow-up† at least at month 2, month 6, month 12, and every year for 5 years; specialist consultations: dermatology, ophthalmology, ear, nose, and throat examination, gynaecology, psychiatry, pulmonology
DRESS	Drug withdrawal, no RCT-validated curative treatment‡; topical or systemic corticosteroids (or both) according to disease severity	Symptomatic, antipyretics	1–10%	Acute organ failure, virus reactivation, relapses	Autoimmune diseases, lupus, thyroiditis, diabetes, scleroderma	Patch testing at month 6; follow-up† at month 2, 3, 4, 5, 6, and 12, then annually
AGEP	Drug withdrawal, no RCT-validated curative treatment; topical or systemic corticosteroids (or both) according to disease severity	Symptomatic, antipyretics, no antibiotics	1%	Recovery	None described	Patch testing after 6 weeks

SCAR=severe cutaneous adverse reaction. SJS=Stevens-Johnson syndrome. TEN=toxic epidermal necrolysis. RCT=randomised controlled trial. DRESS=drug reaction with eosinophilia and systemic symptoms. AGEP=acute generalised exanthematous pustulosis. *Thalidomide increased mortality in an RCT that was stopped early; the benefits of intravenous immunoglobulins and systemic corticosteroids are still being debated; a single-arm trial[73] found some benefits of ciclosporin. †Follow-up is adapted to disease severity and sequelae, a multidisciplinary approach is mandatory for all cases of SJS and TEN and often necessary for DRESS syndrome. ‡Intravenous immunoglobulin had no benefit; the antiviral ganciclovir provided no clear benefit in case reports.

***Table 3*: SCAR management, outcomes, and main sequelae**

藥害救濟給付案之前五大藥品不良反應統計 (1)

(1999 –2025.8)

*不含預防接種受害救濟案件

不良反應類別	性別		總計	症狀分類	小計
	女	男			
Skin and subcutaneous tissue disorders 皮膚及皮下組織疾患	885	813	1698 (66.59%)	Stevens Johnson Syndrome 史蒂文生氏-強生症候群	873
				Toxic Epidermal Necrolysis 毒性表皮壞死溶解症(包含SJS/TEN overlap)	326
				Drug reaction with Eosinophilia and Systemic Symptoms 藥物疹合併嗜伊紅血症及全身症狀	218
				Other 其他	281
Hepatobiliary disorders 肝膽疾患	95	127	222 (8.71%)	Hepatitis (急性)肝炎	87
				Hepatic failure (急性)肝衰竭	56
				Drug-induced liver injury 藥物性肝傷害	26
				Fulminant Hepatitis 猛爆性肝炎	24
				Other 其他	29
Immune system disorders 免疫系統疾患	94	107	201 (7.88%)	Anaphylactic shock 過敏性休克	158
				Drug hypersensitivity 藥物過敏	26
				Other 其他	17

第1～389次審議會

藥害救濟給付案之前五大藥品不良反應統計 (2)

*不含預防接種受害救濟案件

(1999 –2025.8)

不良反應類別	性別 女	性別 男	總計	藥品不良反應	小計
Blood and lymphatic system disorders 血液及淋巴系統疾患	77	31	108 (4.24%)	Agranulocytosis 顆粒性白血球減少症	36
				Pancytopenia 全血球減少症	28
				Thrombocytopenia 血小板減少症	12
				Neutropenia 嗜中性球減少症	10
				Leukopenia 白血球低下症	7
				Other 其他	15
Nervous system disorders 神經系統疾患	42	46	88 (3.45%)	Neuroleptic malignant syndrome 抗精神病藥物惡性症候群	18
				Encephalopathy 腦病變	7
				Cerebral infarction 腦梗塞	6
				Hypoxic-ischaemic encephalopathy 缺氧性腦病變	5
				Other 其他	52

藥害救濟給付案之可疑藥品前十名 (1999 –2025.8)

排名	藥品成分	案例數
1	Allopurinol	283
2	Rifampin/Isoniazid/Pyrazinamide (單方或複方)	162
3	Phenytoin	160
4	Carbamazepine	146
5	Diclofenac	110
6	Co-trimoxazole	93
7	Lamotrigine	70
8	Ibuprofen	68
9	Sulfasalazine	66
10	Mefenamic acid	63

Characteristics of SCAR cases

Gender	M : F = 5 : 6	
Age (years)	26~83 (Mean: 59.7, Median: 63)	
Mortality	9% (Due to invasive pulmonary aspergillosis with respiratory failure)	
Types of SCAR	SJS/TEN: 5	AGEP: 1
	DRESS: 5	GBFDE:0

Culprit drugs

Definite	Volrustomig	1	TMP/SMX (Baktar)	1
	Atezolizumab	1	Phenytoin	1
	(Volrustomig: anti-PD-1/CTLA-4 bispecific antibody; Atezolizumab: anti-PD-L1 antibody)			
Possible	Azithromycin	1	Diclofenac	2
	Cefazolin	1	Piroxicam	1
	Cephradine	2		
	Cefoxitin	1		
	Ceftazidime	1		
	Cefexime	1	Baclofen	1
	Tazocin	1	Broen-C	1
	Esomeprazole	1	諾諾養肺治嗽散	1
	Rabeprazole	1	*(Purchased from the radio station*	
	Pantoprazole	1	*瓶身標註成分：桔梗、川石斛、半夏、川貝母、蘇子、茯苓、薄荷、杏仁 、桑白皮、橘紅、穀芽、甘草、冰片*	
	Alogliptin	1	**Without a license for traditional Chinese medicine, its ingredients cannot be verified.)*	
	Dapagliflozin	1		
	Carbamazepine	1		

A case of cytomegalovirus reactivation involving the skin in a patient with trimethoprim-sulfamethoxazole–induced drug reaction with eosinophilia and systemic symptoms

王姿婷醫師/王盈湘醫師/林尚宏醫師

Kaohsiung Chang Gung Memorial Hospital

Chief complaint

- **37 y/o male with alcohol use disorder**
  (6 bottles of beer per weekend for 20+ years)
- No other systemic underlying diseases
- Body weight: 52kg
- Referred to our hospital with a **2-week history of fever, acute hepatitis with severe jaundice**, and a **generalized itchy rash**
- Vital signs at ER:
  BP: 165/113mmHg; HR:91rpm; BT:36.6'C; SpO2: 99% in room air
- Associated symptoms: no chills, odynophagia, cough, rhinorrhea, shortness of breath, abdominal pain, diarrhea, dysuria, or arthralgia

=> Admitted to GI ward

2024/02/28 KCGMH ER			
WBC	11700	Na	130
Segment	80	K	4.1
Eosinophil	4.0	BUN	17.9
Hb	9.6	Cr	0.54
MCV	88.1	**ALT**	**232**
PLT	466	**AST**	**105**
PT	14.9	**T-bil**	**30.8**
INR	**1.43**	**D-bil**	**19.9**
APTT	38.7	**ALP**	**998**
		GGT	**829**
		Ammonia	46
		ALB	3.77
		CRP	30.81

Hepatitis-related surveys

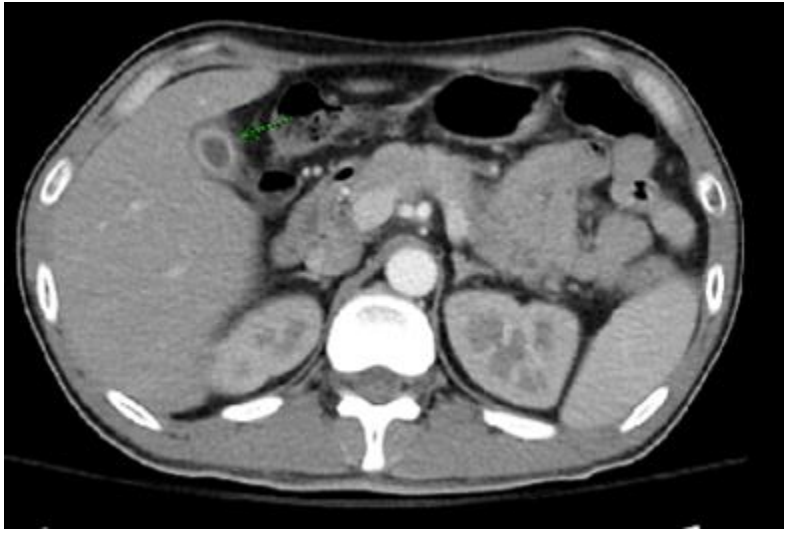
HSV-1 IgG	negative	index
HSV-2 IgG	positive	index
VZV-IgM	negative	index
VZV-IgG	negative	mIU/mL
CMV-IgM	**nonreactive**	Index
CMV-IgG	**reactive**	AU/mL
EB-VCA IgM	negative	U/mL
EB-VCA IgG	negative	U/mL
Anti-HAV IgM	nonreactive	COI
HBsAg	nonreactive	COI
Anti-HBs	nonreactive	IU/L
Anti-HBc IgM	nonreactive	COI
Anti-HCV	nonreactive	COI
HIV combo test	nonreactive	COI
Dengue PCR/Ag	negative	-

Free T4	0.72	ng/dL
TSH	0.584	uIU/mL
ANA	**negative**	-
Anti-dsDNA	**negative**	WHOunit/mL
Anti-mito	**negative**	
ENA screen	**negative**	ratio
IgG	582	mg/dL
IgG4	53	mg/dL
T-chol	419	mg/dL
TG	510	mg/dL
Ceruloplasmin	76.5	mg/dL
Ferritin	10270	ng/mL
AFP	3.2	

Hepatitis-related surveys

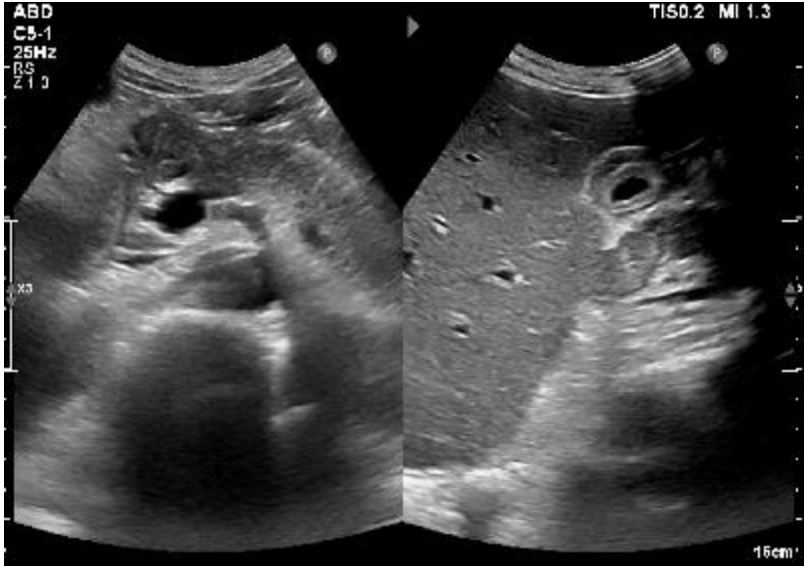
2024/2/28 Abdominal CT

- **Thickening of gallbladder wall <u>without</u> obstructive biliary duct dilatation**, maybe due to acute hepatitis, Dengue fever or other secondary etiology?
- Minimal ascites in the pelvis



2024/3/4 Abdominal echo

- Liver: smooth surface
- No liver mass
- No hepatomegaly/splenomegaly
- Parenchymal liver disease (score 5)
- Mild ascites



Laboratory findings

Empiric flomoxef(2/29-3/1), ceftazidime(3/2-3/6)

Spiking fever

2024	02/28	03/04	03/06	Unit
WBC	11700	7400	10500	/uL
Segment	80	67	67.6	%
Eosinophil	4.0	**14.2**	**15**	%
Hb	9.6	7.9	7.8	g/dL
MCV	88.1	88.9	88.9	fL
PLT	466	286	335	1000/uL
PT	14.9	15.1	14.9	sec
INR	1.43	1.46	1.43	-
APTT	38.7	-	51.2	sec

2024	02/28	03/01	03/04	03/06	Unit
Na	130	128	-	-	mEq/L
K	4.1	3.9	-	-	mEq/L
BUN	17.9	12.0	-	8.8	mg/dL
Cr	0.54	0.40	-	0.51	mg/dL
ALT	**232**	**185**	**92**	**80**	U/L
AST	**105**	**93**	**55**	**75**	U/L
T-bil	**30.8**	**27.2**	**21.5**	**19**	mg/dL
D-bil	**19.9**	**17.5**	**-**	**13.1**	mg/dL
ALP	**998**	**812**	**-**	**844**	U/L
GGT	**829**	**785**	**508**	**-**	U/L
Ammonia	46	-	93	89	ug/dL
Lipase	-	131.1	-	50	U/L
Amylase	-	177	-	95	U/L
ALB	3.77	3.21	2.79	2.7	g/dL
CRP	30.8	38.9	-	83.4	mg/L
LDH	-	234	-	307	U/L

Consult infectious specialist (2024/03/06)

< Impression >

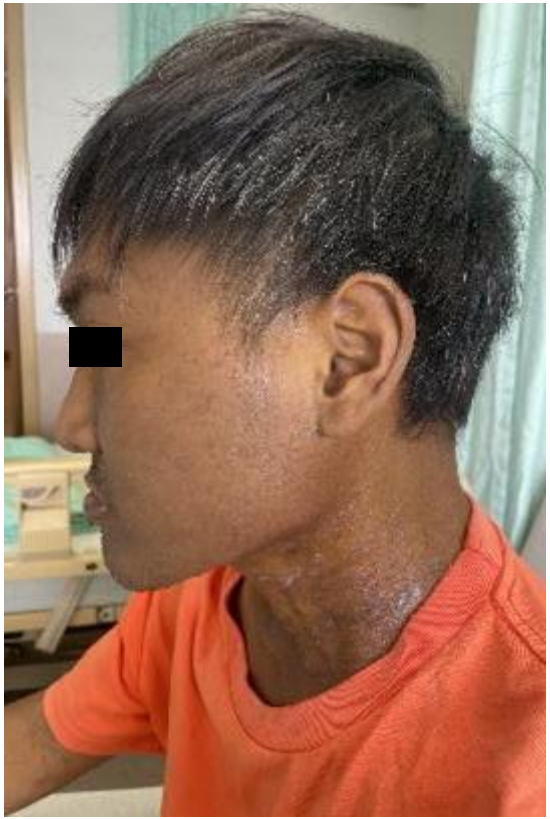
 # Fever, focus to be determined, r/o atypical infection

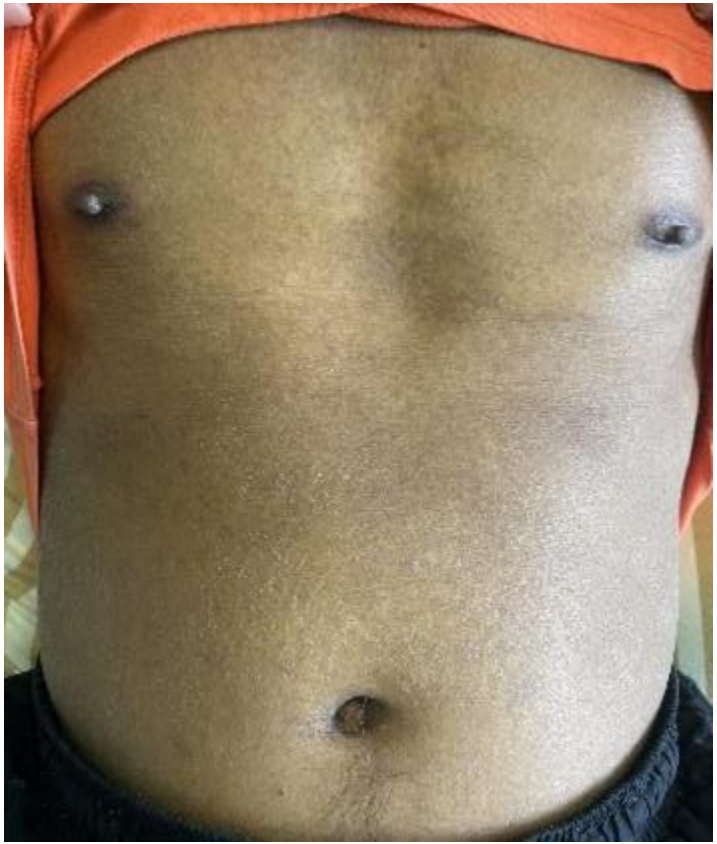
 # Eosinophilia, cause?

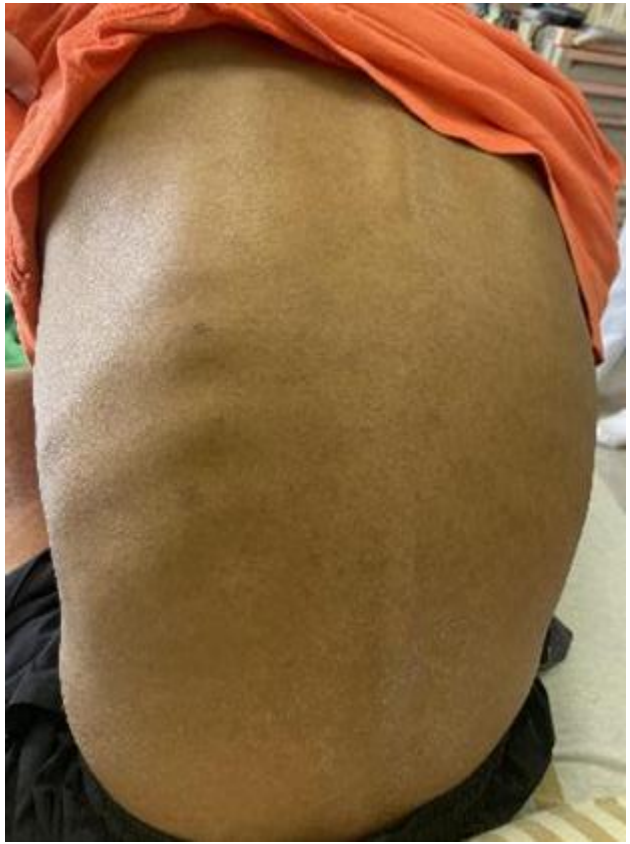
 # Acute liver injury with hyperbilirubinemia, condition improving

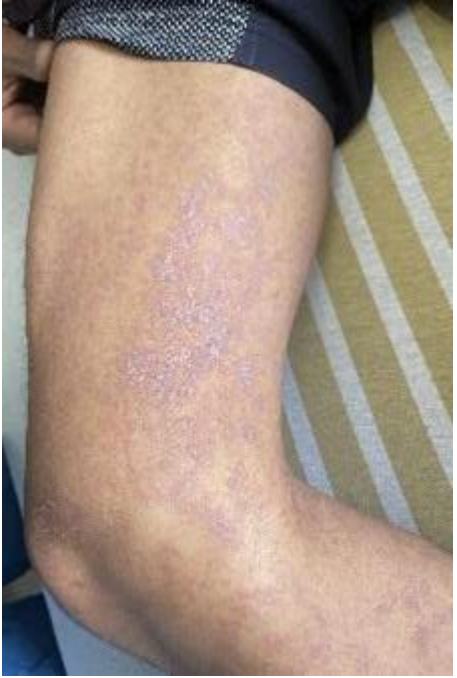
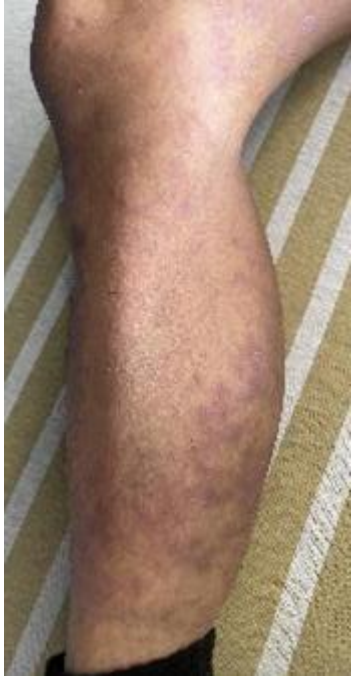
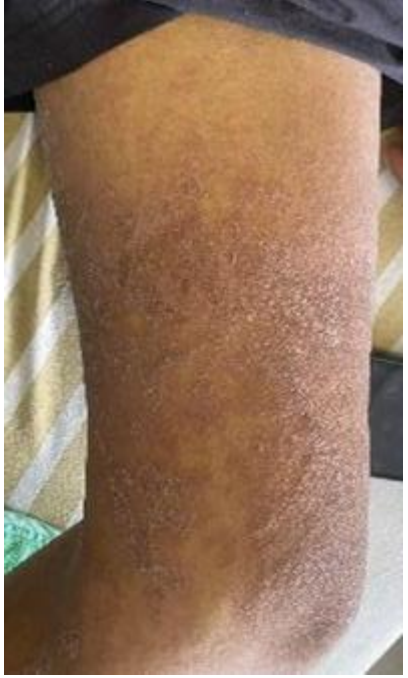
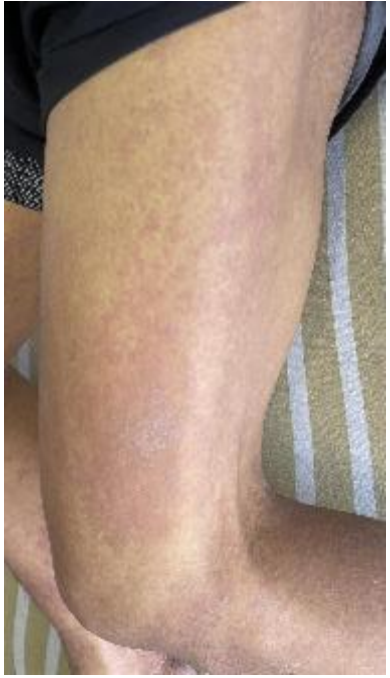
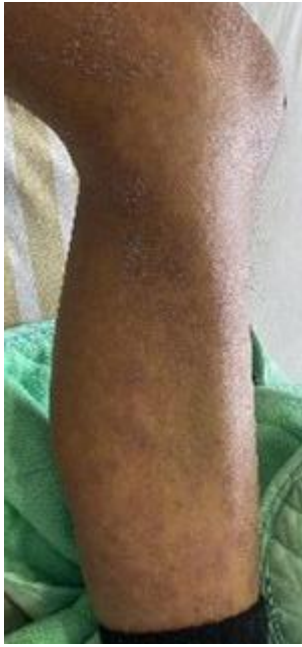
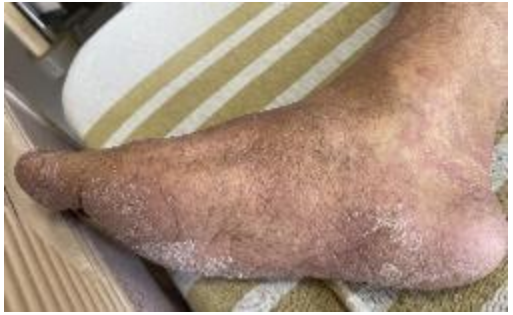
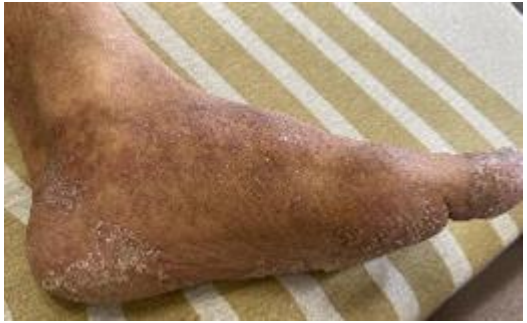
< Suggestion >

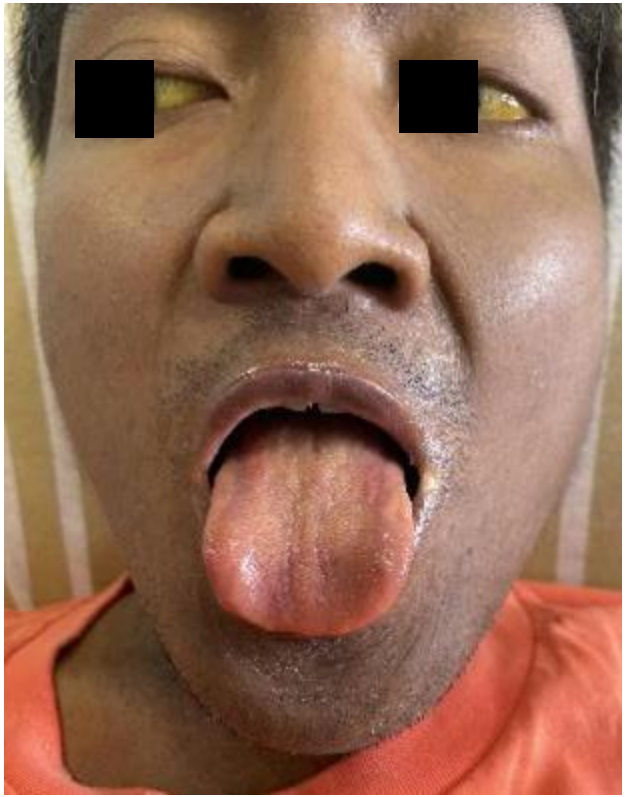
- **Consult derma for evaluation of skin rash** (vasculitis? DRESS?)
- Check SARS-CoV2 rapid Ag test and influenza A+B, Repeat CXR because of fever
- Check serum CMV DNA PCR
- Arrange cardiac echo for evaluation of IE
- 通報鉤端螺旋體 恙蟲病 地方性斑疹傷寒
- Switch antibiotics into ceftriaxone 1g Q12H + doxycycline 1# BID









Present illness

- Denied exposure to topical medications/Chinese herbs
- Denied past allergic histories to food or drugs
- Denied family history of autoimmune diseases

Bleeding during ejaculation
-> Prostatitis diagnosed at LMD

2023/12/03
LMD

Baktar
Doxycycline

Present illness

- Denied exposure to topical medications/Chinese herbs
- Denied past allergic histories to food or drugs
- Denied family history of autoimmune diseases

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- Denied exposure to topical medications/Chinese herbs
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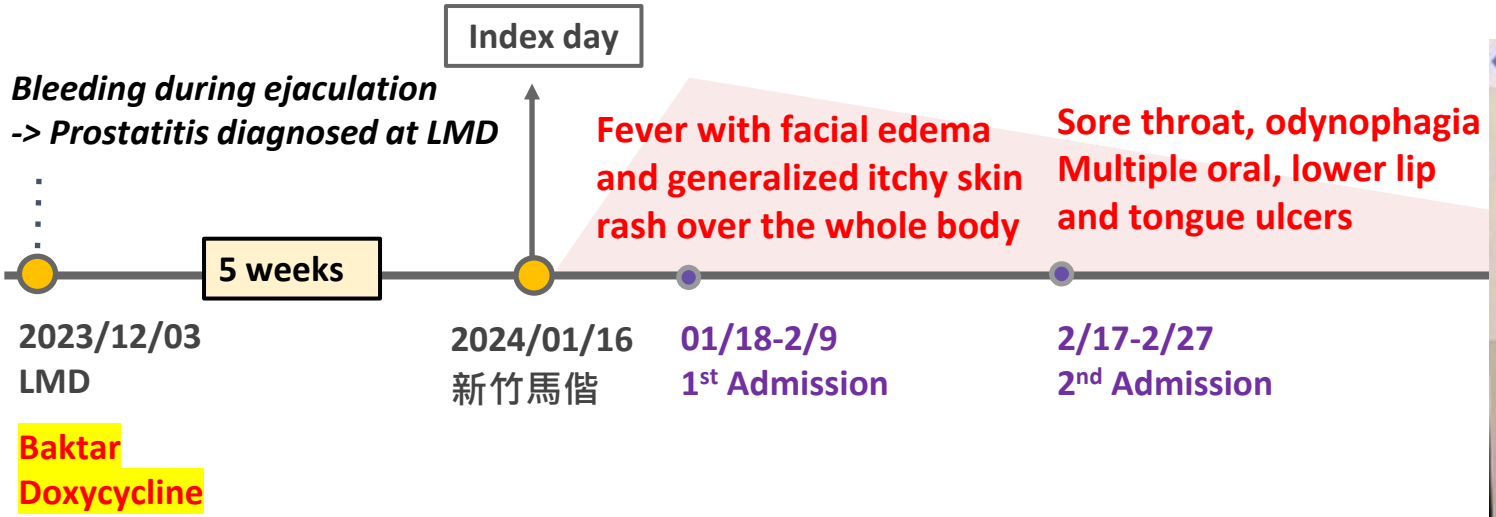

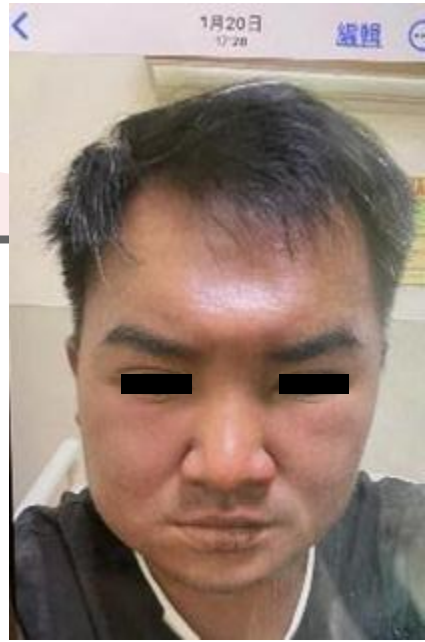

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- Denied exposure to topical medications/Chinese herbs
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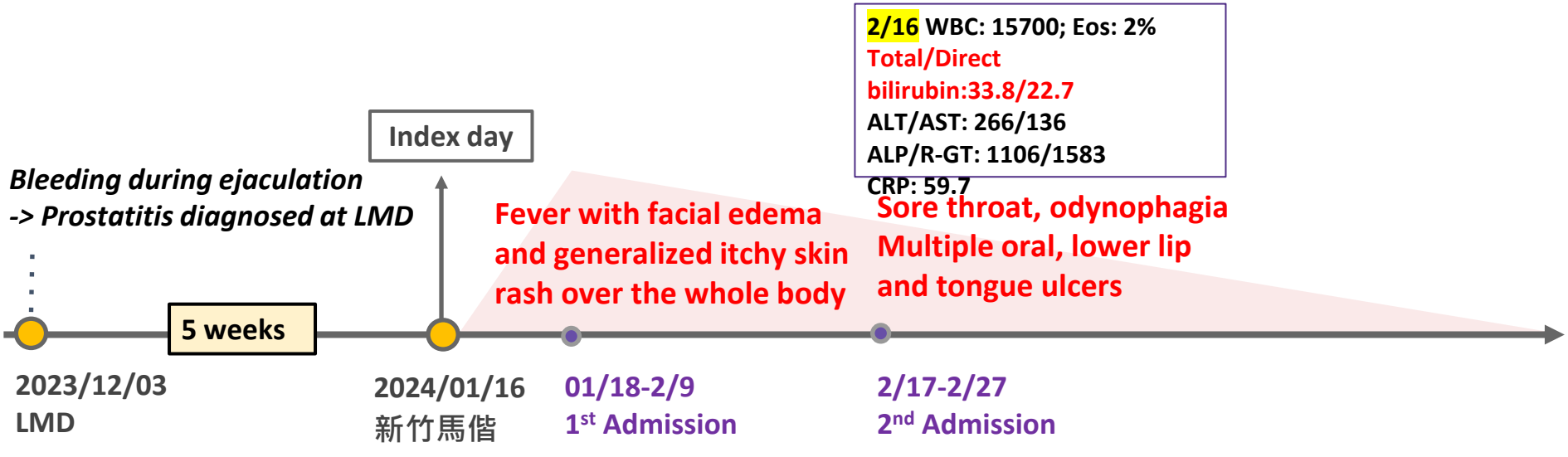
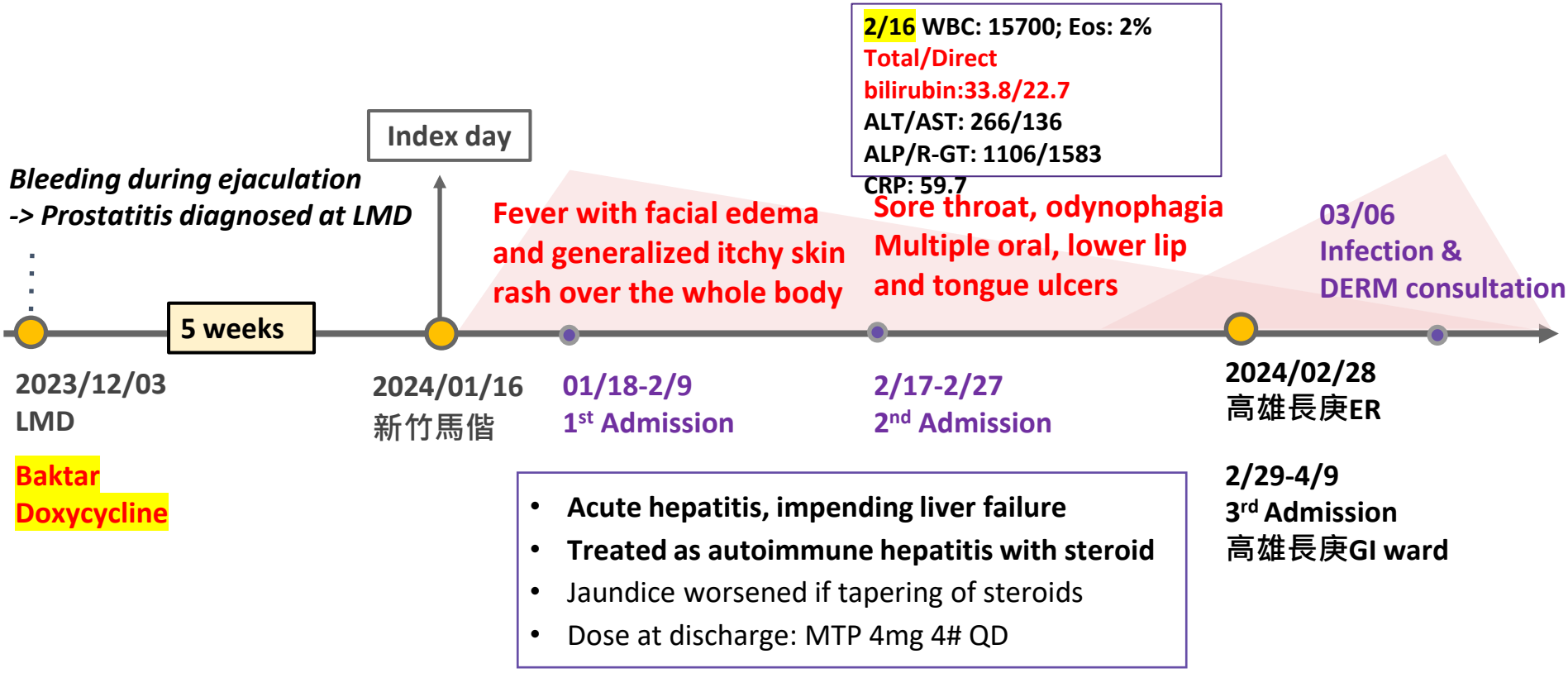


- **Acute hepatitis, impending liver failure**
- **Treated as autoimmune hepatitis with steroid**
- Jaundice worsened if tapering of steroids
- Dose at discharge: MTP 4mg 4# QD

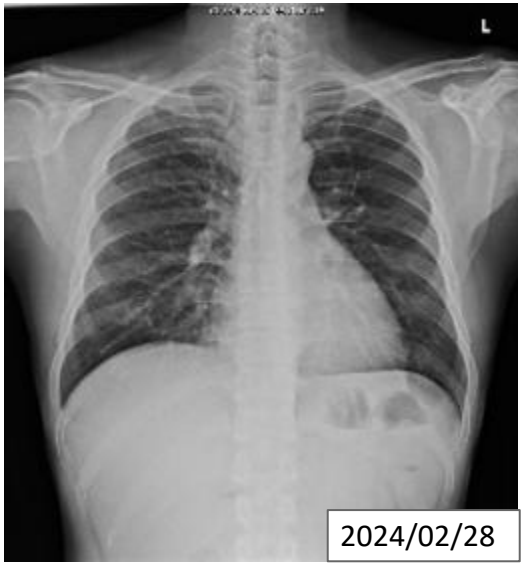
Present illness

- Denied exposure to topical medications/Chinese herbs
- Denied past allergic histories to food or drugs
- Denied family history of autoimmune diseases



Occult infection-related surveys

- Chest XRAY (02/28) : multiple nodular densities over bilateral lung fields
- Blood culture (02/28, 03/06) : no growth
- Urine routine (03/06) : bilirubinuria, no pyuria
- Cardiac echo (03/07) : no vegetation
- Scrub typhus, endemic typhus, spirochetes (03/06): all negative



Clinical impression

Drug reaction with eosinophilia and systemic symptoms (DRESS), RegiSCAR score: 6

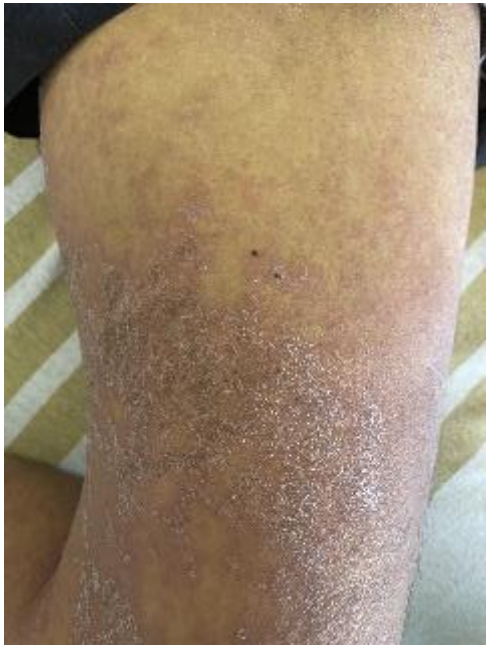
* Index day: 2024/01/16

* **Culprit drug: suspected baktar or doxycycline**

Arrange **skin biopsy** over left thigh on 3/8

Perform **HLA-B gene analysis**

Arranage **liver biopsy** on 3/13



RegiSCAR score (for DRESS)

項目	分數			補述
	-1	0	1	
發燒 ≥ 38.5 ˚C (Fever ≥ 38.5˚C)	N/U	Y		
淋巴結腫大 (Enlarged lymph nodes)		N/U	Y	> 1cm 且 ≥ 2個不同的地方
嗜伊紅性白血球增多 (Eosinophilia)		N/U	Y	Eos count ≥ 0.7 x 10^9/L 或當WBC < 4 x 10^9時 Eos 比例≥ 10% 2分: Eos count ≥ 1.5 x 10^9/L 或當WBC < 4 x 10^9時 Eos比例 ≥ 20%
不典型淋巴球 (Atypical lymphocytes)		N/U	Y	
皮疹 體表面積(TBSA)>50%		N/U	Y	典型DRESS皮疹包含至少兩個以下的特徵：purpuric lesions(other than legs), infiltration, facial edema, psoriasiform desquamation
典型DRESS皮疹	N	Y/U		
皮膚切片與DRESS相符	N	Y/U		
內在器官侵犯 (Organ involvement)		N	Y	1種器官得1分，最多2分
皮疹 ≥ 15天	N/U	Y		
排除其他原因		N/U	Y	排除以下至少3種原因可得1分：HAV, HBV, HCV, Mycoplasma, Chlamydia, ANA, blood culture

Adapted from: Int J Mol Sci. 2017 Jun 9;18(6):1243

Total score:

- <2: Excluded
- 2 to 3: Possible
- 4 to 5: Probable
- ≥6: Definite

Total score: 6

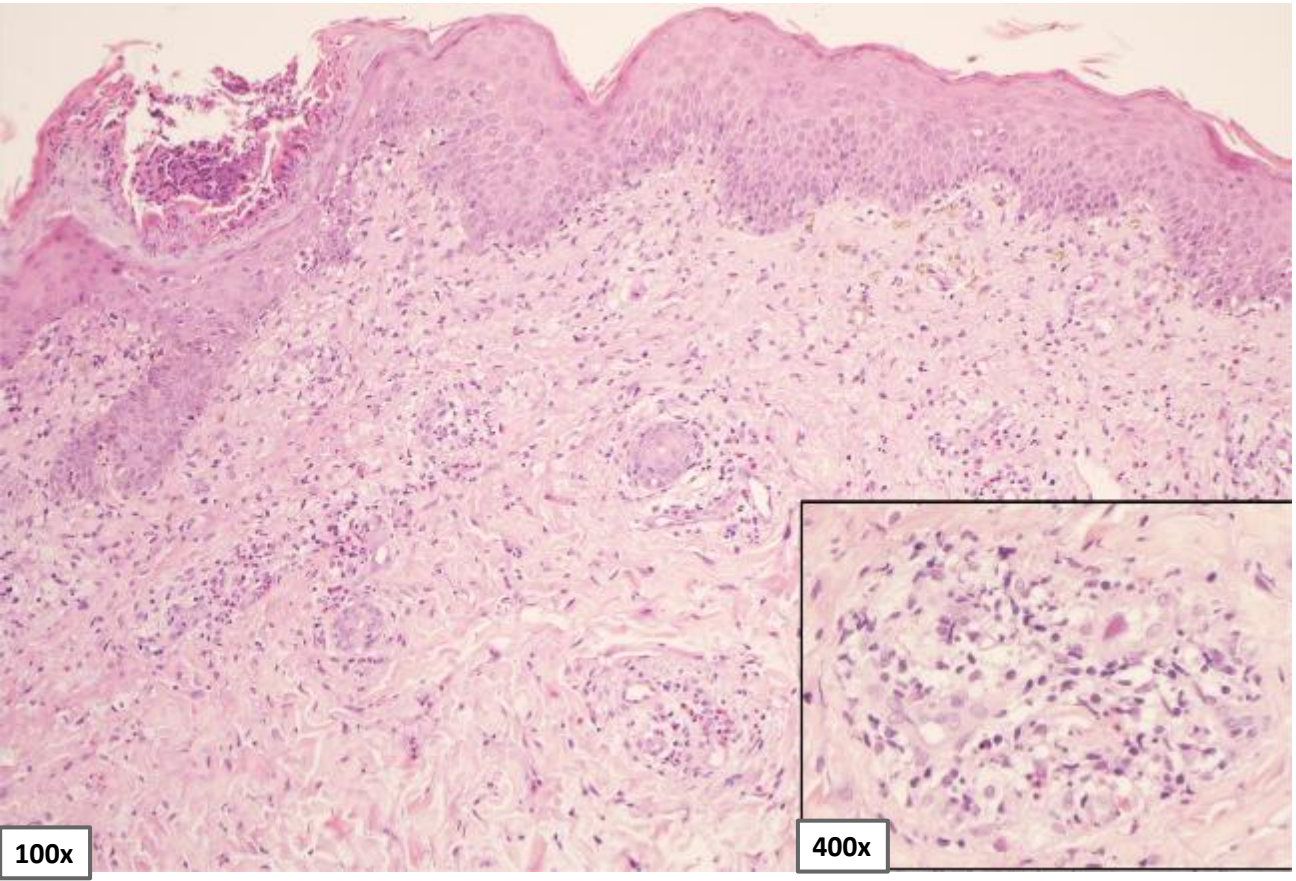
ALDEN score

ALDEN score	Baktar	Doxycycline
Delay from initial drug component intake to onset of reaction	+2	+2
Drug present in the body on index day	0	0
Prechallenge/rechallenge	0	0
Dechallenge	0	0
Type of drug (notoriety)	+3	+2
Other cause	0	-1
Final score	+5	+3

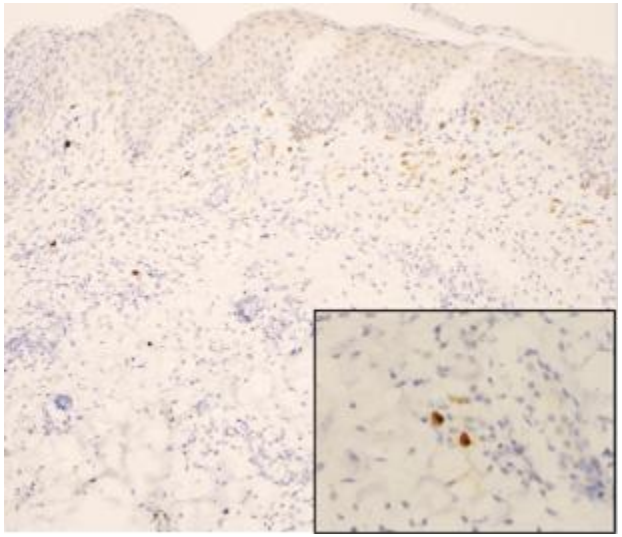
<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.

Pathology report (skin)

1. **Interface dermatitis with eosinophils, c/w DRESS**
2. **Cytomegalovirus infection**



- **Cytopathic effect in endothelial cells**
- **IHC study for CMV : positive**



Pathology report (liver)

Acute hepatitis, suspicious for drug-related injury

- The section shows liver tissue with preserved lobular architecture.
- The portal areas show focal bile duct injury and mild chronic inflammatory cell infiltration including a few eosinophils.
- The hepatic lobules show ballooning change, ground-glass cytoplasm and focal multinucleated giant cell formation of hepatocytes.
- Intracytoplasmic and intracanalicular bile stasis are also evident.
- No obvious plasma cell infiltration is seen.

Impression on clinicopathological correlation and lab data

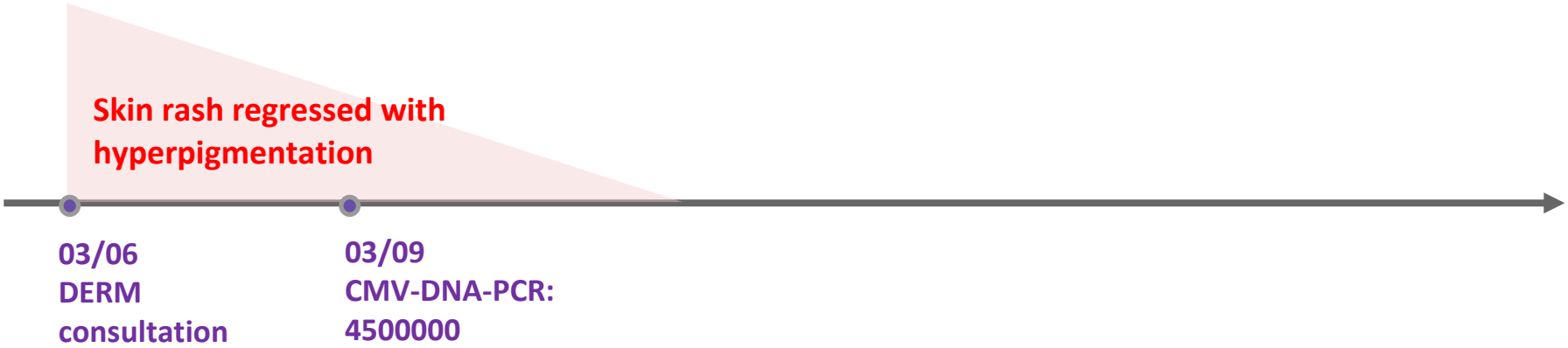
- ✓ **Serum quantitative CMV DNA PCR : viral load of 4,500,000 IU/mL**
- ✓ **HLA-B gene analysis : HLA-B*13:01 genotype**

 # DRESS induced by trimethoprim-sulfamethoxazole (TMP-SMX), complicated by CMV reactivation with CMV viremia and skin involvement

* Index day: 2024/01/16

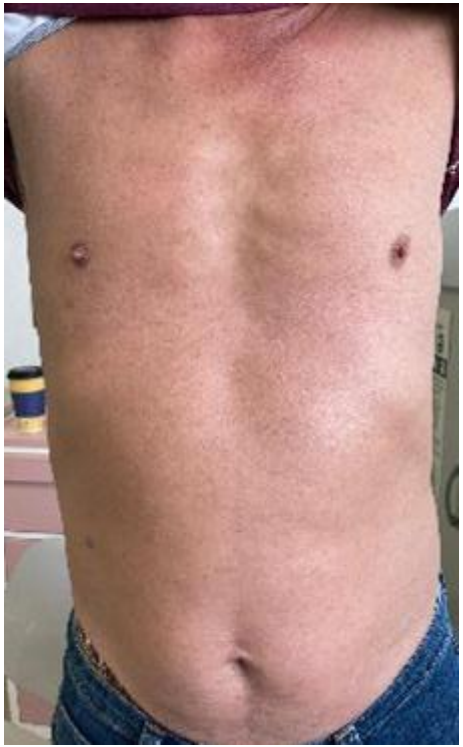
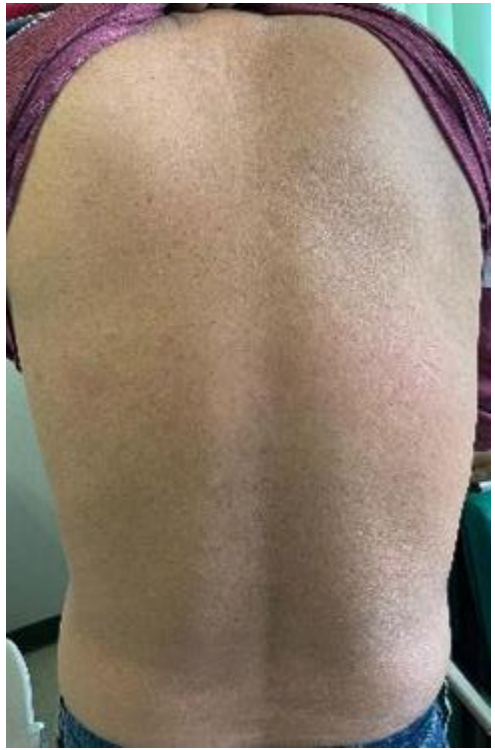
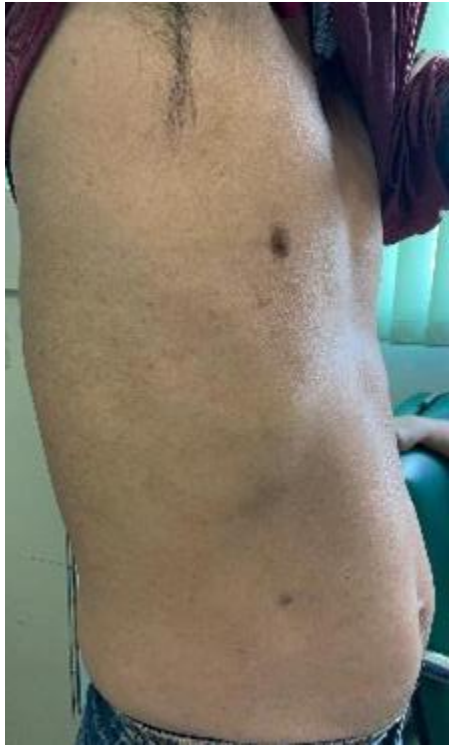
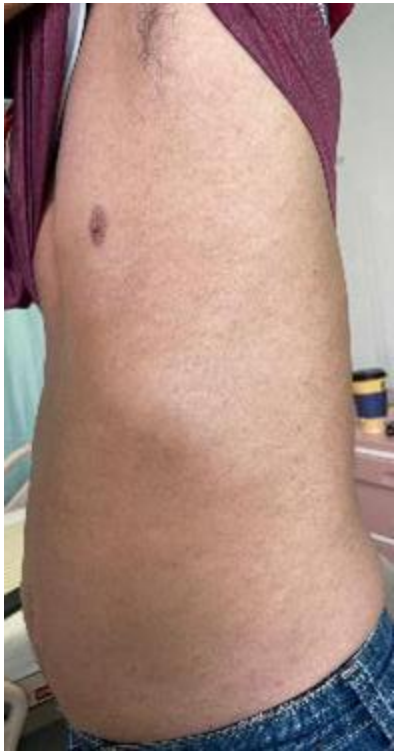
* RegiSCAR score: 6

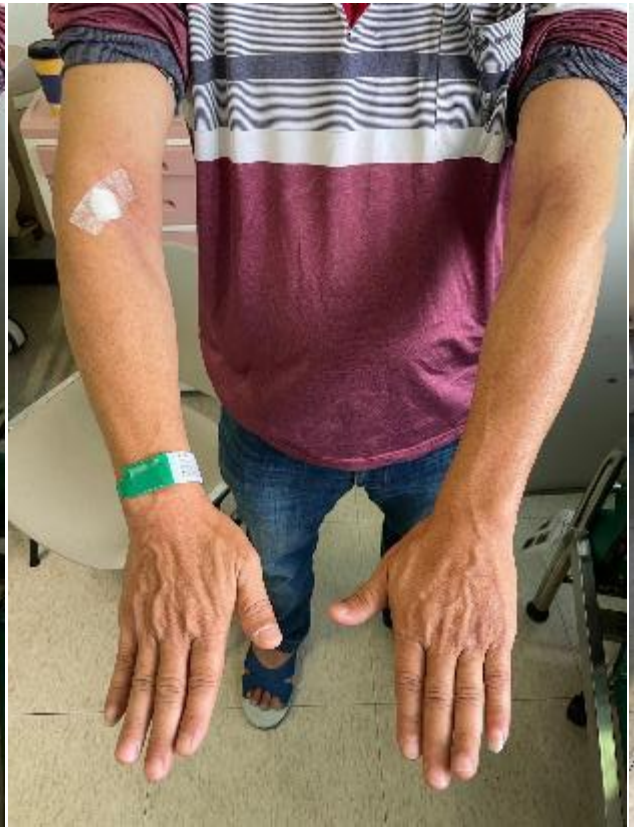
Treatment



IV methylprednisolone (3/7-3/9 40mg Q12H → 3/10-3/12 40mg QD → 3/13-3/31 20mg QD)
→ **oral prednisolone** 10mg BID (4/1-)

IVF Ganciclovir (3/9-3/28 250mg Q12H, 3/29-4/1 250mg QD)
→ **oral Valganciclovir** 900mg QD (4/2-4/24)


Treatment

Liver function tests gradually improved

Total bilirubin: 17.3→ **5.1** (4/8) → **5.8** (4/24)

ALT/AST: 266/136 →**171/86** (4/8) → **119/70** (4/24)

ALP: 838→ **883** (4/8)

Ammonia: 93→ **156** (4/8) → **80** (4/24)

INR: 3.37→**0.91** (4/8)→ **0.9** (4/24)

CRP: 108 → **6** (4/8) → **50.7** (4/24)

CMV viral load decreased **4500000** →**230** (3/28)→ **negative** (4/17)

Persistent leukocytosis and eosinophilia

WBC/eos: 14900/14% (3/13)→ **9400/26%** (4/1)→**13400/7.6%** (4/17)

Skin rash regressed with hyperpigmentation

03/06
DERM consultation

03/09
CMV-DNA-PCR: 4500000

04/09
Discharge

IV methylprednisolone (3/7-3/9 40mg Q12H → 3/10-3/12 40mg QD → 3/13-3/31 20mg QD)
→ **oral prednisolone** 10mg BID (4/1-)

IVF Ganciclovir (3/9-3/28 250mg Q12H, 3/29-4/1 250mg QD)
→ **oral Valganciclovir** 900mg QD (4/2-4/24)

Treatment

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ALT/AST: 266/136 →171/86 (4/8) → **119/70** (4/24)

ALP: 838→ 883 (4/8)

Ammonia: 93→ 156 (4/8) → **80** (4/24)

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CRP: 108 → 6 (4/8) → **50.7** (4/24)

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Persistent leukocytosis and eosinophilia

WBC/eos: 14900/14% (3/13)→ **9400/26%** (4/1)→**13400/7.6%** (4/17)

Skin rash regressed with hyperpigmentation

Newly onset of fever, productive cough, and dyspnea

03/06 DERM consultation

03/09 CMV-DNA-PCR: 4500000

04/09 Discharge

04/17 Infection OPD

04/24 Infection OPD

4/27-5/6 4th Admission

Infection ward

IV methylprednisolone (3/7-3/9 40mg Q12H → 3/10-3/12 40mg QD → 3/13-3/31 20mg QD)

→ **oral prednisolone** 10mg BID (4/1-)

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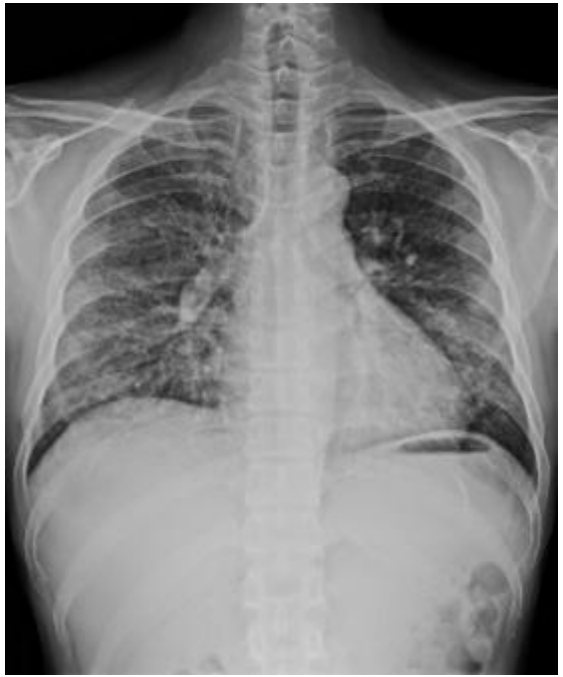
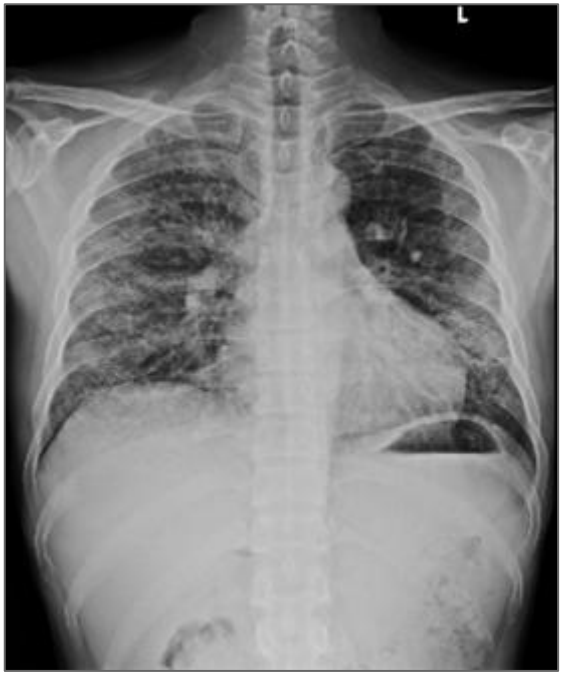
→ **oral Valganciclovir** 900mg QD (4/2-4/24)

Pneumonia-related surveys

4/24 bilateral lower lung infiltration



4/29 progression



	4/24	4/29
WBC	9300	8500
Segment	-	77
Eosinophil	-	4.0
Cr	-	0.45
ALT	119	92
AST	70	63
T-bil	5.8	3.4
D-bil	-	2.3
CRP	50.7	19

Influenza/COVID-19 antigen: negative

GrB. Strep/Legionella/Mycoplasma: negative

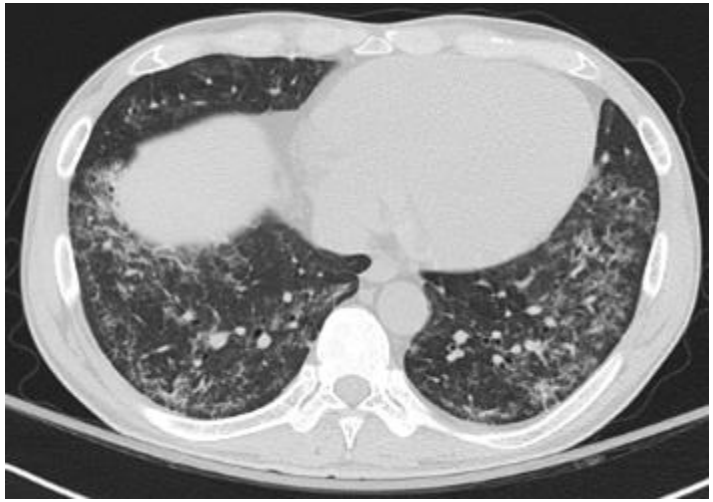
Blood/Sputum culture: negative

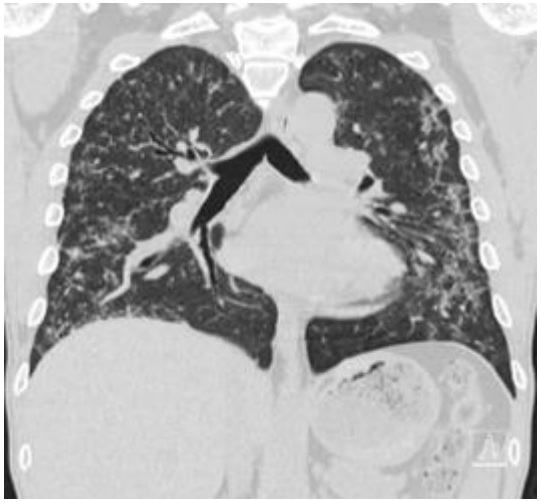
PJ PCR (sputum): negative

Quantiferon test: negative

Pneumonia-related surveys

5/2 HRCT of the Lung





* **Diffusely increased interstitial thickness over the bilateral lung**, the **lower lobe** is more dominant, **compatible with interstitial lung disease**
* Bronchiectasis over bilateral lung mild

5/6 Bronchoalveolar Lavage (BAL)

Cloudy appearance

Gram Stain: No bacteria seen

Aerobic/Anaerobic culture: Negative

Fungus culture: Negative

TB culture: Negative

TB PCR: Negative

PJPCR: Negative

Legion.PCR: Negative

CMV shell vial culture: Negative

Aspergillus Ag: 0.04

Cryptococcus Ag: Negative

Following condition

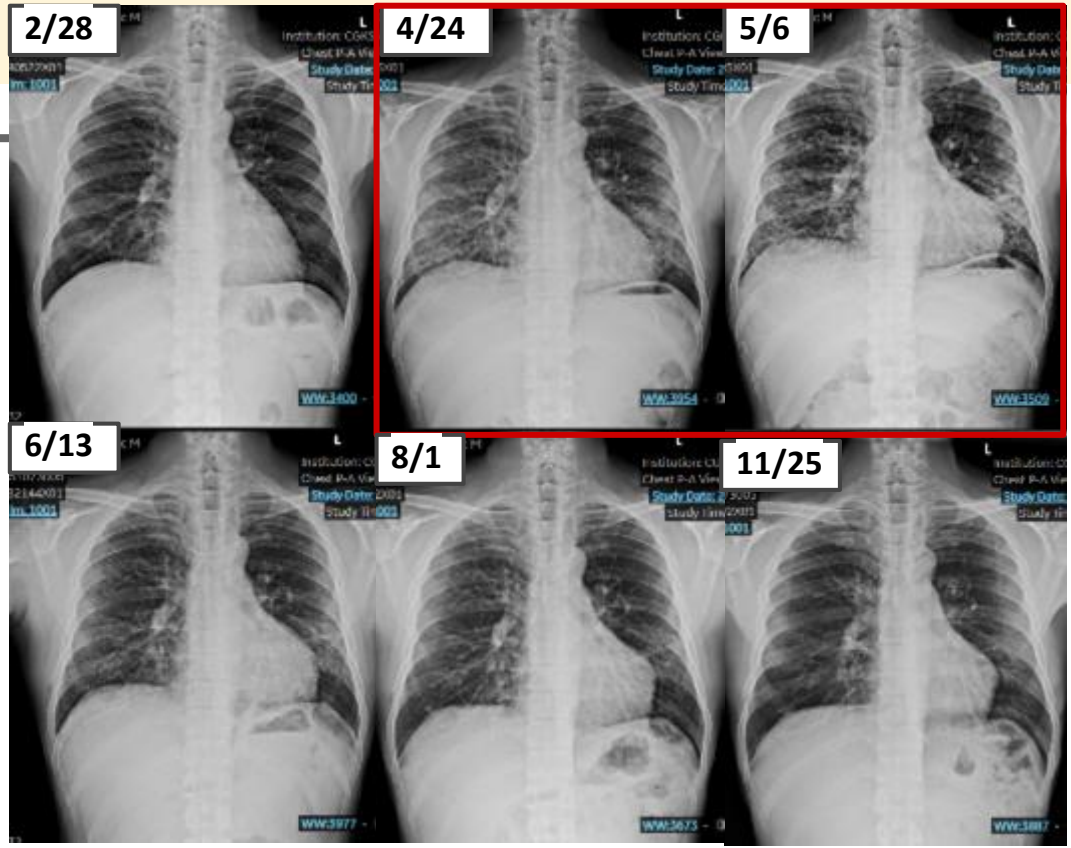
4/27-5/6

4th Admission due to dyspnea

(no recurrent skin lesion)

->**suspect DRESS related interstitial lung disease**

	5/16	6/27	7/4	8/1
WBC	11500	18000	15100	14600
Segment	47.4	-	-	-
Eosinophil	**14.1**	-	-	-
ALT	146	109	110	114
AST	107	75	71	65
T-bil	3.3	7.8	6.0	2.8
PT	9.5	9.9	10.2	9.7



Oral methylprednisolone (4/27-4/30 4mg BID → 4/30-8/1 4mg QD
→ 8/2-8/29 4mg QOD → 8/30-9/26 4mg Q3D → 9/26-10/17 4mg QW)

Summary

A case of DRESS induced by trimethoprim-sulfamethoxazole (TMP-SMX), complicated by CMV reactivation with CMV viremia and skin involvement

- **CMV reactivation in DRESS**:
  - Primarily due to **immune dysregulation** caused by both the illness and the triggering medications
  - Typically occurs **3 to 7 weeks** and becomes **overtly detectable 4 to 5 weeks** after the onset of DRESS
  - **Cutaneous CMV is rare** and can present as morbilliform, urticarial, purpuric, vesicular, or ulcerative lesions. It may be **associated with disseminated infections**.
  - **Uncontrolled viral replication that can lead to serious complications**, including pneumonitis, gastrointestinal issues, and myocarditis, highlighting the need for early intervention
  - **Consider quantitative PCR for CMV in severe or refractory cases**
  - **Management: first-line antiviral agents – intravenous ganciclovir or oral valganciclovir**

Conclusions

- Antibiotic induced cutaneous adverse events, appropriate specialty assessment is indicated to prevent future ADR-related morbidity and mortality.
- This assessment includes defining the most likely drug implicated in the allergic reaction, the probable mechanism(s), and the potential cross-reactive drugs that should be avoided in the future.

Conclusions

- Early recognition and diagnosis of SCARs are key in the identification of culprit drugs.
- SCARS are potentially life threatening, and associated with various clinical patterns and morbidity during the acute stage of Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reactions with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis.
- Early drug withdrawal is mandatory in all SCARs.
- Physicians' knowledge is essential to the improvement of diagnosis and management, and in the limitation and prevention of long-term sequelae.

Thanks for your attention!