Common allergy problems and Drug allergy

ผศ. พญ. ทิชา ฤกษ์พัฒนาพิพัฒน์
อนุสาขาโรคภูมิแพ้ อิมมูโนวิทยาและโรคข้อ
ภาควิชาอายุรศาสตร์ รพ.รามาธิบดี

OUTLINE

- Allergic/ hypersensitivity reaction
  - Specific immune response to allergen: immediate (IgE-mediate), delayed (T cell-mediated, IgG-, eosinophil-, etc)
- IgE-mediated allergic disease
  - Immediate systemic reaction: Anaphylaxis
  - Chronic allergic diseases: Allergic rhinitis, asthma, atopic dermatitis, conjunctivitis
- Urticaria, angioedema
  - Multi-mechanism, mostly non-specific histamine release
- Delayed-type HSR (T cell-mediated)
  - Drug exanthem, SJS-TEN, DRESS

SJS, Stevens-Johnson syndrome
TEN, toxic epidermal necrolysis
DRESS, drug reaction with eosinophilia and systemic symptoms

CUTANEOUS ADVERSE DRUG REACTION (CADR)

T cell-mediated, delayed-type hypersensitivity (DTH)

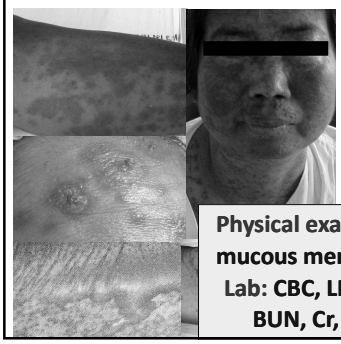
Clinical Classification of Drug Allergy

	Immediate	Nonimmediate
Onset	< 1 hour	>1 hour (usu. >24 hr)
Mechanism	Mostly IgE-mediated	T cell-mediated
Cutaneous	Urticaria, angioedema	Maculopapular rash, bullous, pustular
Systemic symptoms & signs	Hypotension, wheezing, dyspnea, diarrhea	Fever, hepatitis, nephritis, pneumonitis Hematologic involvement

Demoly P, Bousquet J. Allergy 2002; 57 (suppl.72):37-40

Nonimmediate (mostly T cell-mediated)

Visible



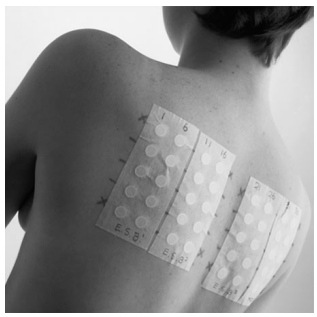
Physical exam: V/S, mucous membrane
Lab: CBC, LFT, UA, BUN, Cr, CXR

Not visible:

- Fever
- Hepatitis
- Cytopenia
- Leukocytosis, eosinophilia
- Nephritis
- Pneumonitis
- Internal organ vasculitis

Patch test

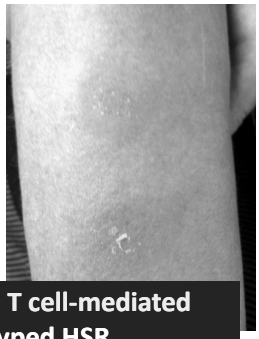
Diagnosis of type IV (T cell-mediated) DTH



Read at 48, 96 hours

Intradermal test (IDT) – delayed reading

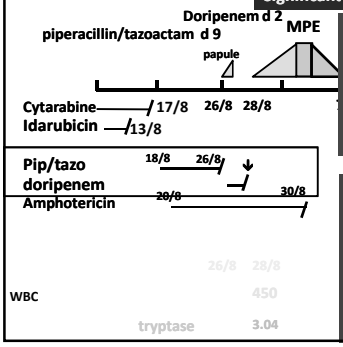
- Perform intradermal skin test
- Delayed reading (48 h up to 7 days): eczema, infiltrative lesion



Confirm Type IV, T cell-mediated delayed typed HSR

37 year female with relapse AML (maculopapular exanthem; MPE)

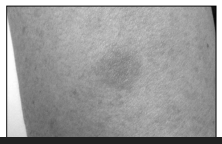
History MPE- vanco, meropenem
Significant MPE: doripenem d2, Pip/tazo d9 (off 2d)



- DDx MPE from infection แต่เลี่ยง piperacillin/tazobactam, doripenem, meropenem
- Graded or desensitization to BL ที่จะใช้
- นัด test เมื่อ stable

4 months later: β-lactam testing

- Relapse AML after SCT 5 yr, S/P chemoRx → CR
- Suspected drug reaction
  - MPE from meropenem (d9), vancomycin (d6)
  - papule from Tazocin (d9)
  - MPE from doripenem (d2)
- ST pen/pip-tazo/carbapenem (delayed-reading) :
  Positive pip/tazo
- DPT meropenem: negative
- DPT vancomycin: negative

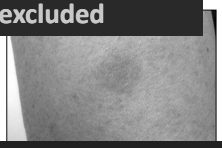


Infiltrative papule at pie/tazo 20 hr after testing

4 months later: β-lactam testing

Diagnosis: type IV HSR to piperacillin/tazobactam
History of MPE (meropenem and vancomycin) can be excluded

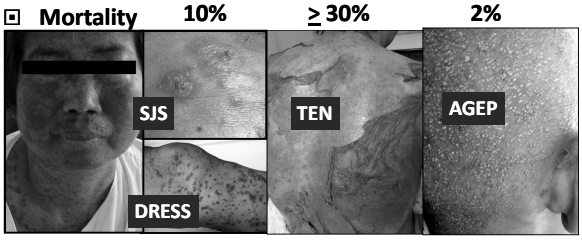
- MPE from doripenem (d2)
- ST pen/pip-tazo/carbapenem (delayed-reading) :
  Positive pip/tazo
- DPT meropenem: negative
- DPT vancomycin: negative



Infiltrative papule at pie/tazo 20 hr after testing

Severe Cutaneous Adverse Reaction (SCAR)

- Mortality 10% ≥ 30% 2%

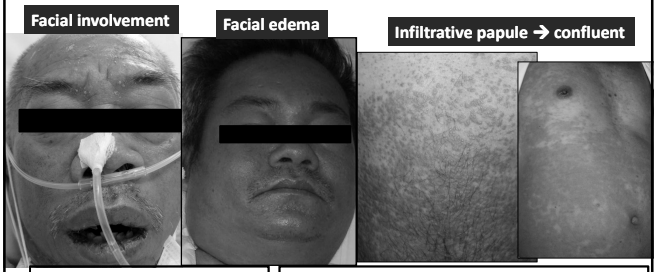


Only 'early withdrawal of suspected drug' could decrease mortality rate[1]

Importance of early diagnosis!

1. Garcia-Doval I, et al. Arch Dermatol 2002; 136:323-7.
SJS-TEN, Stevens-Johnson syndrome; AGEP, acute generalized exanthematous pustulosis
DRESS, drug reaction with eosinophilia and systemic symptoms

Red flag Symptoms & Signs for non-immediate HSR



Laboratory results:
- Leukocytosis, eosinophilia, atypical lymphocytosis
- Hepatitis

General symptoms:
- Fever, myalgia, arthralgia, lymphadenopathy

Non-specific but good 'warning sign'

Bircher AJ. Toxicology 2005;209:201-7.

54 year male, eye pain and lip swelling 2 days → rash

2 days ago: eye & lip pain with lip swelling, Rx: amoxycillin, idarac, steroid E.D. → next day: generalized rash

- PH: Gout for 4 months colchicine- rash
- Current Rx (3 weeks ago): celecoxib as needed, allopurinol (300) 1x1

Mucous mb ulceration

Flat, purpuric macules, irregular shape (SJS)

Diagnosis: SJS (allopurinol day 21)

Clinical Classification of SJS-TEN

	Pattern of lesions	Distribution	Extent of blisters / Detachment %	Mortality
Erythema Multiforme major (EMM)	Raised (typical or atypical targets)	Localized (acral)	< 10	0%
SJS	Flat atypical targets or Blister on macules	Widespread	< 10	10%
Overlap SJS-TEN	Flat atypical targets or Blister on macules	Widespread	10-29	10-30%
TEN with spots	Flat atypical targets or Blister on macules	Widespread	≥ 30	30+%
TEN without spots	no discrete lesion, Large erythematous area	Widespread	≥ 10	30+%

Bastuji-Garin S, …. and Roujeau J-C. Arch Dermatol 1993; 129:92-96.

Clinical Classification of SJS-TEN

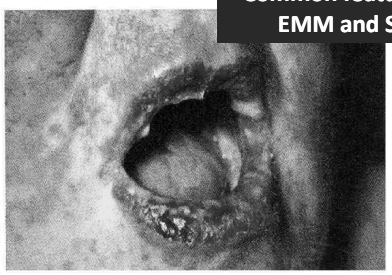
Recognition 2 common skin eruption in SJS-TEN:
Macule and atypical target
All with epidermal necrolysis (bleb or detachment)

Erythema Multiforme major (EMM)	Raised (typical or atypical targets)	Localized (acral)	< 10	0%
SJS	Flat atypical targets or Blister on macules	Widespread	< 10	10%
Overlap SJS-TEN	Flat atypical targets or Blister on macules	Widespread	10-29	10-30%
TEN with spots	Flat atypical targets or Blister on macules	Widespread	≥ 30	30+%
TEN without spots	no discrete lesion, Large erythematous area	Widespread	≥ 10	30+%

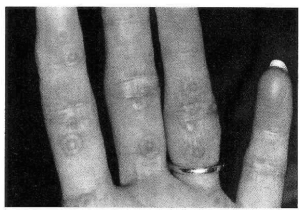
Bastuji-Garin S, …. and Roujeau J-C. Arch Dermatol 1993; 129:92-96.

Importantly 'mucous membrane involvement'

Common feature of both EMM and SJS-TEN

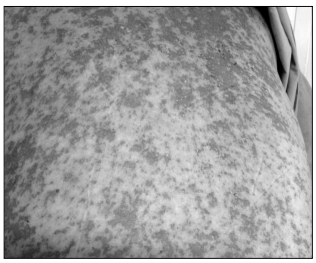


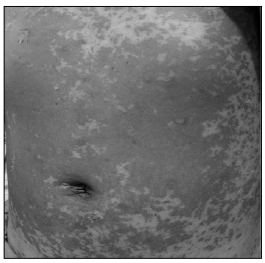
EMM (Erythema multiforme major)



- 'Iris' lesion: circular, raised, 3 zones lesion
- Typically acrally localized
- Association with viral infection
- No mortality

Purpuric Macules in SJS



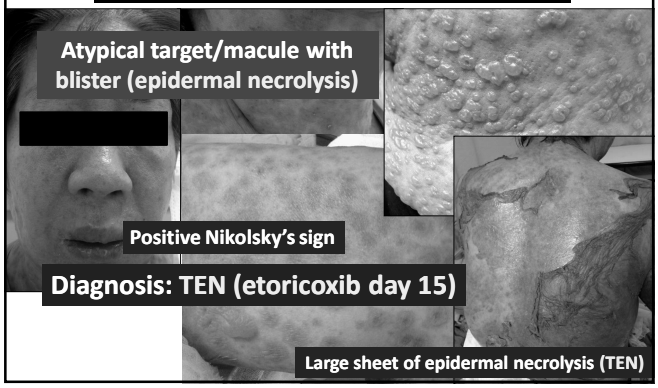


- Most common in SJS-TEN
- Flat, purpuric macules
- Irregular shaped

• May develop confluent erythema →epidermal necrolysis and detachment

Early sign = Nikolsky's sign

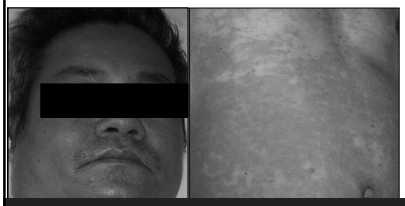
Female with fever, exanthema eruption, oral and eye pain for 4 days



50 year male with fever, diarrhea, pruritic rash and jaundice for 6 days

RA (1st diagnosis): SSZ, etoricoxib, CQ, pred, INH, OMZ for 6 wks
MTX, folic for 4 days

T 38.3 C, BP 130/90 mmHg, HR 110/min, RR 20/min
Face swelling and confluent maculopapular eruption



CBC: Hct 41%, WBC 22,700 (N56%, L17%, M 12%, E14%) Plt 159,000/mm³

LFT: AST 52, ALT 72, AP 735, GGT 874 U/L, TB 6.7, DB 4.8 mg/dl

UA: Sp gr 1.025, prot 2+, WBC 10-15, no eosinophil, RBC 2-3, granular cast 2-4, waxy cast 0-1, epith 5-10/HPF

BUN 23 mg/dl, Cr 1.2 mg/dl

Diagnosis: DRESS (likely sulfasalazine)

Criteria for DIHS/DRESS

Modified from J-SCAR and EuroSCAR

1. MP rash begins > 3 wks after initiation of drug
   - Suggestive: BSA > 50%, facial swelling, exfoliative dermatitis **2**
2. Prolonged clinical symptoms > 2 wks after stop the drug
3. Fever (> 38 C)
4. Transaminase > 100 U/L [2x of normal value] **1**
5. Leukocyte abnormalities (at least one)
   - Leukocytosis (> 11,000 cell/mm³) [high or lower than norm] **1**
   - Atypical lymphocytosis (> 5%) [any %] **1**
   - Eosinophilia (> 1,500 cell/mm³) [> 10-20%, AEC > 700-1500] **2**
6. Lymphadenopathy **1**
7. HHV 6 reactivation

Score 4-5 (probable)
≥ 6 (definite)

Shiohara T et al. Br J of Dermatol 2007; 156:1045–1092.
Kardaun SH, et al. Br J Dermatol 2007; 156: 609-611.

Common Drug Lists

SJS/TEN

- Allopurinol
- Carbamazepine
- Phenytoin
- Phenobarbital
- Lamotrigine
- Sulfamethoxazole
- Nevirapine
- Oxicam, coxib?

DRESS

- Anti-convulsant
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Lamotrigine
- Allopurinol
- Sulfonamides
  - Sulfasalazine, dapsone
- Abacavir, nevirapine
- Minocycline, vancomycin

Roujeau JC, et al. N Engl J Med 1995;333:1600-7.

Take Home Message

- **Hypersensitivity:** excessive function → autoimmune disease, allergic disease
- **Allergy (Type I, IgE-mediated immediated HSR)**
  - Systemic: Anaphylaxis → adrenaline IM
  - Chronic inflammation: AR, asthma → topical steroid
- **Pseudoallergy:** pre-meds + slow rates
  - Isolated angioedema: look for drug (ACE-I, NSAIDs)
- **Delayed (Type IV, T-cell mediated)**
  - Maculopapular exanthem: avoid
  - SJS-TEN, DRESS: early recognition, avoid

Culprit: allopurinol, antiepileptic drug, sulfonamide, anti-retroviral drug

- V/S, mucous mb, epidermal necrolysis
- CBC, LFT, UA, CXR
- Daily visit