**Common allergy problems and Drug allergy**

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**OUTLINE**

- **Allergic/hypersensitivity reaction**
  - Specific immune response to allergen: Immediate (IgE-mediated), 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

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**Clinical Classification of Drug Allergy**

<table>
<thead>
<tr>
<th>Onset</th>
<th>Immediate</th>
<th>Nonimmediate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 1 hour</td>
<td>&gt;1 hour (usu. &gt;24 hr)</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Mostly IgE-mediated</td>
<td>T cell-mediated</td>
</tr>
<tr>
<td></td>
<td>Urticaria, angioedema</td>
<td>Maculopapular rash, bullous, pustular</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Hypotension, wheezing, dyspnea, diarrhea</td>
<td>Fever, hepatitis, nephritis, pneumonia</td>
</tr>
<tr>
<td>Systemic symptoms &amp; signs</td>
<td>Internal organ involvement</td>
<td></td>
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</tbody>
</table>

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

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**CUTANEOUS ADVERSE DRUG REACTION (CADR)**

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

**NonImmediate** (mostly T cell-mediated)

- **Visible**
  - Fever
  - Hepatitis
  - Cytopenia
  - Leukocytosis, eosinophilia
- **Not visible:**
  - Nephritis
  - Pneumonitis
  - Internal organ vasculitis

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

**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**

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

- **Infiltrative papule at pip/tazo 20 hr after testing**

**Severe Cutaneous Adverse Reaction (SCAR)**

- **Mortality**
  - 10% > 30% 2%

Only ‘early withdrawal of suspected drug’ could decrease mortality rate

- **Importance of early diagnosis**

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**37 year female with relapse AML**

**[maculopapular exanthem; MPE]**

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

- **Cytarabine**
- **Idarubicin**
- **WBC**
- **Trypsin 3.04**

- **Pip/tazo**
- **doripenem**
- **Amphotec**

- **40k**
- **WBC**
- **Trypsin 3.04**

**4 months later: β-lactam testing**

- **Diagnosis**: type IV HSR to pipercillin/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 pip/tazo 20 hr after testing**

- **Red flag Symptoms & Signs for non-immediate HSR**

- **Facial involvement**
- **Facial edema**
- **Infiltrative papule → confluent**

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

- **General symptoms:**
  - Fever, myalgia, arthralgia, lymphadenopathy

- **Non-specific but good ‘warning sign’**

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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 (5 weeks ago): celecoxib as needed, allopurinol (300) 1x1

**Diagnosis:** SJS (allopurinol day 21)

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### Clinical Classification of SJS-TEN

<table>
<thead>
<tr>
<th>Pattern of lesions</th>
<th>Distribution</th>
<th>Extent of blisters / Detachment %</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema Multiforme major (EMM)</td>
<td>Raised (typical or atypical targets)</td>
<td>Localized (acral)</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>SJS</td>
<td>Flat atypical targets or Blister on macules</td>
<td>Widespread</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Overlap SJS-TEN</td>
<td>Flat atypical targets or Blister on macules</td>
<td>Widespread</td>
<td>10-29</td>
</tr>
<tr>
<td>TEN with spots</td>
<td>Flat atypical targets or Blister on macules</td>
<td>Widespread</td>
<td>≥ 30</td>
</tr>
<tr>
<td>TEN without spots</td>
<td>no discrete lesion, Large erythematous area</td>
<td>Widespread</td>
<td>≥ 10</td>
</tr>
</tbody>
</table>

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**Importantly 'mucous membrane involvement'**

**Common feature of both EMM and SJS-TEN**

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### EMM (Erythema multiforme major)

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

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### 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
**Famila with fever, exanthema eruption, oral and eye pain for 4 days**

- Atypical target/macule with blister (epidermal necrolysis)
- Positive Nikolsky’s sign
- Diagnosis: TEN (etoricoxib day 15)

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

- RA (1st diagnosis): SSZ, etoricoxib, CO, 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

**Criteria for DIHS/DRESS**

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

Score 4-5 (probable) ≥ 6 (definite)


**Common Drug Lists**

- **SJS/TEN**
  - Allopurinol
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Lamotrigine
  - Sulfamethoxazole
  - Nevirapine
  - Oxicam, coxib?

- **DRESS**
  - Anti-convulsant
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Lamotrigine
  - Allopurinol
  - Steroids
  - Sulfasalazine, dapsone
  - Abacavir, nevirapine
  - Minocycline, vancomycin

**Take Home Message**

- Hypersensitivity: excessive function → autoimmune disease, allergic disease
- Allergy (Type I, IgE-mediated immediate 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

**Question?**

Thank you For your Attention