MECHANISMS OF CUTANEOUS DRUG REACTIONS

Non-immunologic mechanisms (sometimes predictable)
- Overdose
- Pharmacologic side effects
- Cumulative / delayed toxicity
- Drug-drug interactions

Immunologic mechanism (unpredictable)

MECHANISMS OF CUTANEOUS DRUG REACTIONS

Non-immunologic mechanisms (sometimes predictable)
- Overdose
- Pharmacologic side effects
- Cumulative toxicity
- Delayed toxicity
- Drug-drug interactions
- Alterations in metabolism

Idiosyncratic (unpredictable)
- Immunologic / genetic
- DRESS
- SJS/TEN
- Drug reactions in HIV infection
- Drug-induced lupus erythematosus

IMMUNOLOGIC MECHANISMS OF CUTANEOUS DRUG REACTIONS

Gell-Coombs classification
- Type I: IgE-dependent drug reactions: urticaria, angioedema, anaphylaxis.
- Type II: Cytotoxic drug-induced reactions: thrombocytopenia.
- Type III: Immune complex-dependent drug reactions: vasculitis, serum sickness.
- Type IV: Delayed-type, cell-mediated drug reactions: exanthematous, fixed drug eruptions, SJS and TEN, DRESS, acute generalized exanthematous pustulosis (AGEP).

However, Gell-Coombs classification is oversimplified when applied to drug reactions.

DRUG RASH?
DRUG ERUPTION?
Assessment of Drug eruption

- Clinical
- Statistics:
  Which drugs are common?
- Drug Hx and Timing: Drug timeline
  How long after the drug started did the reaction begin?
  Response to withdrawal / rechallenge

Morphological classification of Drug-induced cutaneous eruptions
- Red: Erythematous / purpuric
  Exanthematous (MP), urticarial
- Pustular
- Vesicles bullae erosion
- Simple (Mild) VS Complex (Severe)

Features suggestive of severe cutaneous adverse drug reaction (SCAR)
- Cutaneous
  - Facial involvement - edema or swelling
  - Mucous membrane involvement (erosions / involving conjunctiva)
  - Skin tenderness, skin fragility, blistering or shedding
    “positive Nikolsky sign”
  - Vesicles/ Bullous, pustular lesions, purpura

- Systemic
  - Fever and/or other symptoms of internal organ involvement
  - Lymphadenopathy
  - LAB: eosinophilia, atypical lymphocytes, elevated LFTs, creatinine

Mild or Severe? : SEVERE CUTANEOUS ADVERSE REACTIONS (SCARs)
- Anaphylaxis
- Acute generalized exanthematous pustulosis (AGEP)
- Drug rash with eosinophilia and systemic symptoms (DRESS) / drug induced hypersensitivity syndrome (DIHS)
- Stevens–Johnson syndrome (SJS)
  toxic epidermal necrolysis (TEN)
- Generalized bullous fixed drug eruption (FDE)
- Anticoagulant-induced skin necrosis

Assessment of Drug eruption

- Type of drug reaction / morphology
- Severity
- Statistics:
  Which drugs are most likely to cause that type of reaction?
- Timing:
  How long after the drug started did the reaction begin?
  Response to withdrawal / rechallenge
Literature search
- Textbooks, PubMed
- Litt’s Drug Eruption and Reaction Database
- Data from pharmaceutical companies
- Drug Alert Registry

Assessment of Drug eruption
- Type of drug reaction / morphology
- Severity
- Statistics: Which drugs are most likely to cause that type of reaction?
- Timing: Drug timeline
  How long after the drug started did the reaction begin?
  Response to withdrawal / rechallenge

Typical timing of drug eruptions in relationship to time since drug initiation

Morphological approach
Red lesions

Classic case scenario
- Patient with no known underlying disease
- 1 wk Hx of fever, myalgia, cough, URI symptoms
- Purchased medications from local pharmacy
- Developed skin rash after taking medication

DDx Exanthematous/ maculopapular eruption
- Drug-induced
- Viral exanthem: EBV, CMV, enterovirus, adenovirus, HHV 6, parvovirus B19, acute HIV
- Other infectious exanthem
  - Secondary syphilis
  - Scarlet fever (group A strep)
  - Toxic shock syndrome
  - Early meningococcemia, early rickettsial infection
- Generalized eczema, CNT disease
- Others: Kawasaki disease, graft versus host disease, still’s disease
**DDx maculopapular drug eruption VS viral exanthem**

**Drug**

- **Viral exanthem**
  - Pattern: trunk to peripheral, symmetry (pattern depends on virus)
  - Pruritus: sometimes
  - Duration: resolves within 1-2 weeks

**Drug-induced exanthematous eruption**

- **Child:** 10–20%
- **Adult:** 50–70%

**Symptoms**

- **Pruritus**
- **Duration:** occurs within 1 week of Rx

**Prodromal**

- **Conjunctivitis**
- **Lymphadenopathy**
  - always
- **CBC**
  - Eosinophilia

**Pattern**

- **Prodromal**
  - occurs within 1 week of Rx
  - follows symptoms

**Exanthematous rash**

- **Drug-induced exanthematous eruption**
  - Child: 10–20%
  - Adult: 50–70%

**Symptoms**

- **Pruritus**
- **Duration:** occurs within 1 week of Rx

**Prodromal**

- **Conjunctivitis**
- **Lymphadenopathy**
  - always
- **CBC**
  - Eosinophilia

**Exanthematous drug eruption**

**Morbilliform drug eruption**

**Maculopapular drug eruption**

- **Most common form of drug eruptions**
- **Onset**
  - Occurs within 4-14 days of drug initiation
  - Earlier, within 2-3 days in rechallenge
- **Skin lesions**
  - Symmetrical, typically starts on the trunk and spreads peripherally
  - Mucous membrane spared
- **Symptoms**
  - Pruritus, no systemic involvement

**Urticaria**

- **Wheal & flare**
  - Transient erythematous, edematous papules and plaque
  - Central pallor
  - Pruritus
- **Resolves:** few hours < 24 hrs
- **Resolves with normal skin**
  - Except: urticarial vasculitis \( \rightarrow \) lasts > 24 hrs, resolves with hyperpigmentation

**Management**

- Identify, discontinue offending drug if possible
- High risk medications: aminopenicillins, allopurinol, sulfonamides, cephalosporins, aromatic anticonvulsants
- **Symptomatic Treatment**
  - Oral antihistamines
  - Glucocorticoids: topical or systemic
Urticaria
- Acute urticaria \( \rightarrow \) lasts < 6 week
- Chronic urticaria \( \rightarrow \) lasts > 6 week
- Drugs induce Acute > chronic urticaria

Drug-induced urticaria
The 2nd most common cutaneous manifestation of drug allergy
Occurs within 24 hours of drug ingestion
- Drug-induced urticaria
  - Penicillins
  - Cephalosporins
  - Sulfonamides
  - ASA, NSAID
  - Contrast media

Drug-induced Angioedema
- Angiotensin-converting enzyme (ACE) inhibitors

Treatment
- Withdraw causative drug
- For mild reactions: H1 antihistamines.
- For anaphylactic shock: epinephrine (adrenaline), corticosteroids

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
Drug-induced hypersensitivity syndrome (DISH)

DRESS = Drug Rash with Eosinophilia and Systemic Symptoms
- ONSET 15-40 days
- Fever, Rash, facial edema
- Lymphadenopathy
- Arthralgia
- Hematologic abnormalities: eosinophilia, atypical lymphocytes
- Hepatitis
- Others: myocarditis, interstitial nephritis, interstitial pneumonitis
- Allopurinol
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin, lamotrigine
- Sulfonamides, dapsone
- ARV: Abacavir, nevirapine
- ATBs, anti TB: IRZE

Scoring system for DRESS (drug reaction with eosinophilia and systemic symptoms)
- European Registry of Severe Cutaneous Adverse [Drug] Reactions (RegiSCAR)
DRESS MANAGEMENT

- Severe CAR STOP Medication
- Systemic steroid (Prednisolone 0.5-2 mg/kg/d)

Course Rash and hepatitis
- may persist for weeks after drug is discontinued
- may recur if glucocorticoids are tapered
- Slow tapering dose over 1-3 months

Cutaneous Small-Vessel Vasculitis CSVV

- Clinical: palpable purpuric papules, lower extremities
- Other: urticaria-like lesions, hemorrhagic blisters
- Histology: leukocytoclastic vasculitis (LCV)

Histology: leukocytoclastic vasculitis (LCV)

- Palpable purpura

Bullous vasculitis
Bullae on purpura

Conclusion

DRUG RASH?
DRUG ERUPTION?

Drug-induced vasculitis

- Type II (cytotoxic) or type III (immune complex)
- Usually 7-21 days after drug administration
- Within 3 days if rechallenge
- Lab: systemic vasculitis: UA urinary sediment, abnormal renal function, GI bleeding

Common drug-induced CSVV: penicillins, cephalosporins, NSAIDs, sulfonamides

- Others: propylthiouracil, thiazide diuretics, furosemide, allopurinol, systemic immunomodulators [granulocyte/macrophage colony-stimulating factors (G-CSF, GM-CSF), interferons, TNF α inhibitors]

Cutaneous Adverse Drug Reactions (CADR): Part 1 Erythema and purpura

- Skin lesions: exanthematous/maculopapular, urticarial, purpuric
- Exanthematous/MP eruptions and urticaria are the most common CADRs

- Exanthematous morphology may be mild OR severe: DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)
- Urticarial morphology “wheal and flare” may be mild OR severe: angioedema, anaphylaxis, serum sickness-like reaction
- Palpable purpura: cutaneous small-vessel vasculitis (leukocytoclastic vasculitis) may be drug induced

Thank you for your attention