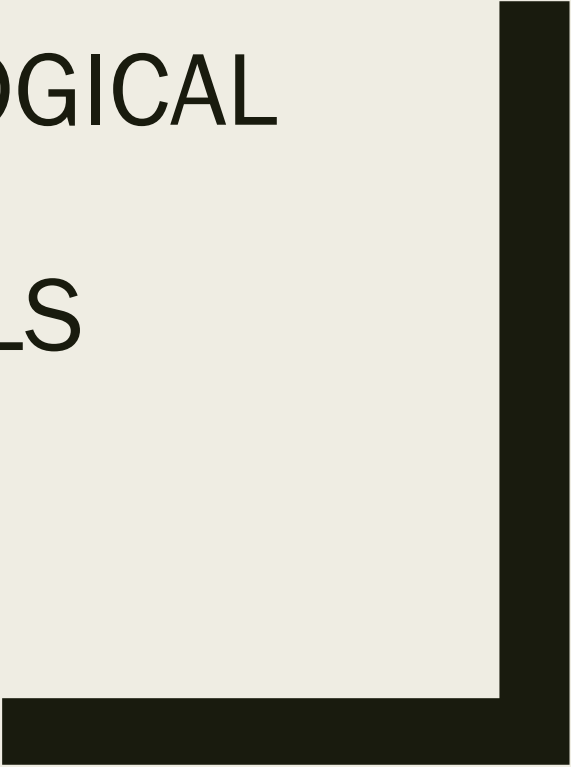


# ADVERSE DERMATOLOGICAL REACTIONS OF PHARMACEUTICALS

Thomas L. Kincheloe IV, OMS III



# Epidemiology:

- Adverse Events due to side effects of drugs occur in about 19% of Hospitalized patients
- Adverse Dermatological Drug Reactions occurred about 2-3% in Hospitalized patients
  - *Most reactions are benign*
  - *Few are fatal*
- Adverse Dermatological Drug Reactions account for approximately 3% of Disabling Injuries occurring during hospitalization

# Classifications of Dermatologic Reactions<sup>1</sup>

## ■ Classic Reactions

- Exanthemas
- Urticaria/angioedema
- Anaphylaxis
- Hypersensitivity vasculitis
- Exfoliative dermatitis/erythroderma
- Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis
- DRESS
- Fixed Drug Reactions
- Photosensitivity/allergy

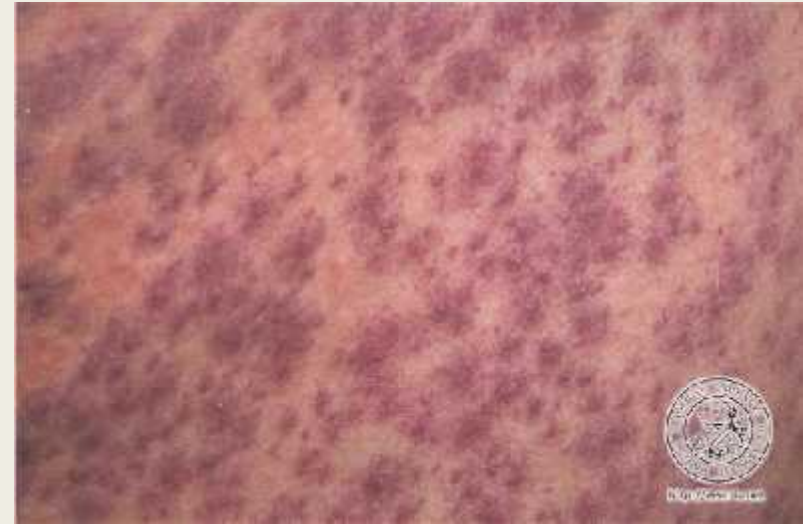
## ■ Uncommon Reactions

- Pemphigus
- Bullous pemphigoid
- Linear IgA bullous dermatosis
- Acute generalized exanthematous pustulosis
- Drug-induced lichen planus
- Alopecia
- Cutaneous pseudolymphoma
- Acral chemotherapy reactions
- Drug-induced lupus

## ■ Special Drug Specific Reactions

# Exanthema

- Skin rash reaction either with characteristic macular or papular features or morbilliform.
- Most Common Offending Agents:
  - *Antibiotics*
    - Penicillin/Cephalosporin
    - Macrolides
    - Quinolones
    - Tuberculostatic
  - *Anticonvulsants*
    - Carbamazepine (Tegretol)
    - Phenytoin (Dilantin)
  - *NSAIDs & Acetaminophine*
  - *Reverse Transcriptase Inhibitors*
    - Nevirapine
    - Abacavir



<http://www.dermis.net/dermisroot/en/13658/image.htm>



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# Urticaria/Angioedema

- Hives or pruritic, circumscribed, raised and erythematous eruptions with central palor
- Angioedema is the swelling of deep dermis and subcutaneous tissue that can cause life-threatening airway obstruction.
- Most Common Offending Agents:
  - *Antibiotics*
    - Penicillin/Cephalosporin
    - Sulfonamides
  - *Opiate Analgesics*
    - Morphine
    - Codeine
  - *“Red man Syndrome”*
    - Rapid infusion of Vancomycin
    - Concomitant use of Opioids and vancomycin



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# Hypersensitive Vasculitis

- Previously named as serum sickness-like reactions or allergic vasculitis
- Criteria for Hypersensitive Vasculitis
  - Age >16 YO
  - Use of a possible offending drug in temporal relation to the Sx
  - Palpable Purpura
  - Maculopapular Rash
  - Biopsy of Skin lesion showing Neutrophils around vasculature
- Most common offending agents:
  - Hydralazine
  - Minocycline
  - Propylthiouracil
  - Levamisole-adulterated cocaine
  - Penicillin/Cephalosporin
  - Sulfonamides
  - Phenytoin
  - Allopurinol



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# Exfoliative Dermatitis/Erythroderma

- Potential life-threatening condition in which scaling of >90% of the skin surface area
- Some patient manifest Exfoliative Dermatitis with DRESS
- Most Common Offending Agents
  - *Allopurinol*
  - *Penicillin*
  - *Barbiturates*
  - *Gold Salts*
  - *Arsenic*
  - *Mercury*



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# Steven-Johnson Syndrome & Toxic Epidermal Necrolysis

- Mucocutaneous eruptions where skin detachment and necrosis occurs.
- SJS is <10% of body surface while TEN is >30% of body surface.
- Most Common Offending Agents
  - *Allopurinol*
  - *Aromatic Anticonvulsants*
    - Diphenylhydantoin (Dilantin Infatabs)
    - Phenobarbital (Luminal)
    - Phenytoin (Dilantin)
    - Carbamazepine (Tegretol)
  - *Antibacterial Sulfonamides*
  - *Lamotrigine (Lamictal)*
  - *Nevirapine*
  - *-Oxicam NSAIDs*



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# Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Severe Fever (100.4-104 °F), Malaise, Lymphadenopathy.
- Visceral Involvement
- Most Common Offending Agents
  - *Aromatic Antiepileptic*
    - Phenobarbital (Luminal)
    - Phenytoin (Dilantin)
    - Carbamazepine (Tegretol)
    - Oxcarbazepine (Trileptal)
  - *Allopurinol*
  - *Lamotrigine (Lamictal)*



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# Fixed Drug Reactions

- Erythematous, edematous plaques with either a grey center or bullae.

- Most Common Offending Agents

- NSAIDs

- ASA
    - Ibuprofen
    - Naproxen
    - Mefenamic Acid

- Antibacterial Agents

- TMP-SMX
    - Tetracyclines
    - Penicillins
    - Quinolones
    - Dapsone

- Barbiturates

- Acetaminophen

- Antimalarials



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<http://www.dermis.net/dermisroot/en/29122/image.htm>

# Phototoxicity

- Direct tissue or cellular damage following UV irradiation of the phototoxic agent.
- Most Common Offending Agents
  - *Tetracyclines*
  - *Thiazides*
  - *Sulfonamides*
  - *Fluoroquinolones*
  - *NSAIDS*
  - *Phenothiazine*
  - *Psoralens*
  - *Griseofulvin*
  - *Voriconazole*
  - *Aminolevulinic acid/methyl aminolevulinate*
  - *Porfimer sodium*
  - *Retinoids*
  - *Tar compounds*
  - *St. John's wort*

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# Phytophotodermatitis

- Phototoxic reaction from plants from specific plant families
  - Apiaceae
    - Celery
    - Wild Parsnip
    - Parsley
    - Dill
    - Fennel
  - Rutaceae
    - Lemons
    - Limes
  - *Ficus carica* (fig tree)
  - *Psoralea corylifolia*

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# Photoallergy

- Delayed-type hypersensitivity when allergen is transformed after exposure to UV radiations.
- Pruritic, eczematous eruptions
- Most Common Offending Agents
  - *Sunscreens*
  - *NSAIDs*
  - *Fragrances*
  - *Phenothiazine*
  - *Antimicrobial agents*
  - *Quinidine*
  - *Griseofulvin*
  - *Quinine*
  - *Quinolones*
  - *Sulfonamides*
  - *Ketoprofen*
  - *Piroxicam*



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# Pemphigus

- Autoimmune flaccid bullous (blisters) that are often painful. Develop along the mucosa, esp. oral cavity.
- Most Common Offending Agents
  - *Penicillamine*
  - *Thiol (SH) compounds*
    - Captopril
    - Piroxicam
  - *Penicillin and derivatives*
    - NOT the Cephalosporins



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# Bullous Pemphigoid

- Tense bullae (blisters)
- Most Common Offending Agents
  - *Penicillamine*
  - *Ferosemide*
  - *Captopril*
  - *Penicillin*
  - *Sulfasalazine*
  - *Salicylazosulfapyridine*
  - *Penacetin*
  - *Nalidixic Acid*
  - *Topical Fluorouracil*
  - *Neuroleptics*



<http://www.dermis.net/dermisroot/en/30060/image.htm>



<http://www.dermis.net/dermisroot/en/29946/image.htm>



<http://www.dermis.net/dermisroot/en/30028/image.htm>

# Linear IgA bullous Dermatitis

- Subepidermal bullous pemphigoid-like lesions. Mucosal/Conjunctival lesions are not present.
- Most Common Offending Agents
  - *Vancomycin*
  - *Lithium*
  - *Cefamandole*
  - *Captopril*
  - *Diclofenac*



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# Acute Generalized Exanthematous Pustulosis

- Rare superficial, nonfollicular, pustules on edematous erythematous on face or intertriginous areas.
- Most Common Offending Agents
  - *Antibiotics*
    - Penicillin
    - Macrolide
  - *Diltiazem*
  - *Antimalarials*



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# Drug-Induced Lichen Planus

- Rare flat, violaceous, pruritic papules
- Most Common Offending Agents
  - *Beta-blockers*
  - *Methyldopa*
  - *Penicillamine*
  - *Quinidine*
  - *NSAIDs*



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# Alopecia

- Hair loss from two mechanisms:
  - Cessation of mitotic activity
    - *Most Common Offending Agents*
      - Antineoplastic agents
  - Premature arrest of the follicle
    - *Most Common Offending Agents*
      - Anticoagulants
      - Retinoids
      - Interferons
      - Antihyperlipidemic



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# Cutaneous Pseudolymphoma

- Benign hyperplasia of few lymphoid infiltrates of the skin. Most are nodular
- Most Common Offending Agents
  - *Antidepressants*
    - Fluoxetine (Prozac)
    - Amitriptylin
  - *Calcium Channel Blockers*
  - *ACE inhibitors*
  - *Antihistamines*
  - *Beta blockers*
  - *Benzodiazepines*
  - *Antihyperlipidemic agents*



# Acral Chemotherapy Reactions

- Dysesthesia in the skin, most often symmetric edema and erythema of the palms and soles. May progress to bullous formation and necrosis.
- Most Common Offending Agents
  - *Cytosine Arabinoside*
  - *Doxorubicin*
  - *Capecitabine*
  - *Docetaxel*
  - *Sunitinib*
  - *Sorafenib*



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# Drug-induced Lupus

- Cutaneous manifestations are less common in drug-induced lupus.
- Most common Sx:
  - *Fever*
  - *Myalgia*
  - *Rash*
  - *Arthralgia*
  - *Arthritis*
  - *Serositis*
- Most Common Offending Agents
  - *Procainamide*
  - *Hydralazine*



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<http://www.dermis.net/dermisroot/en/38892/image.htm>

# Specific Drugs causing Reactions

- Warfarin
- Heparin
- Gold
- Lithium
- Halogenoderma
- Cytokine Therapy

# Warfarin

- Skin necrosis during the first several days due to fibrin thrombi within cutaneous vessels.
- Lesions are usually located on extremities, breasts, trunk, and penis (in males).



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# Heparin

- Delayed-type Hypersensitive skin reaction
  - *Occurs about 2x weeks post heparin induction.*
  - *Localized erythema at injection site*
  - *May progress to eczematous/maculopapular eruption*
- Immediate Hypersensitive skin reaction
  - *Anaphylactic/anaphylatic-like reaction*
  - *Urticaria, hypotension, angioedema, allergic rhinoconjunctivitis, tachycardia, or bronchospasm.*
- Skin necrosis
  - *3-15x days post initiation of Heparan therapy*
  - *Cutaneous necrosis from intradermal microvascular thromboses*

# Gold

- Dermatitis and stomatitis
  - *Nonspecific dermatitis resembling contact dermatitis*
  - *Eruptions last:*
    - Median: 2x months
    - Range: 1x week – 2x years
    - Resolution with prompt discontinuation or dose reduction

# Lithium

- Cutaneous reactions have been reported in 3-34% of patients using lithium
- Of these, the most common types of reactions are:
  - *Psoriasis*
    - Can begin during the first treatment
    - Can exacerbate preexisting
  - *Acne or acneiform eruptions*
    - Pustular lesions
    - Commonly seen in forearms and legs
  - *Hair loss*
    - Usually in women during the first few months of therapy

# Halogenoderma

- Ingestion of Halogens:
  - *Iodides*
    - Seaweed
    - Salt, Amiodarone
    - Radiocontrast Media
  - *Bromides*
  - *Fluoride*
- Symptoms:
  - *Acneiform lesions*
  - *Lesions with varying degrees of ulceration*
  - *Swelling of parotid & submandibular glands.*
- Discontinuation of causative agent results in gradual resolution of lesions in 4-6x weeks.

# Cytokine Therapy

- Injection site reactions are common.
- Specific Agents
  - *Colony-Stimulating Factors*
    - Neutrophilic Dermatoses
    - Variable in morphology
  - *Interferons*
    - Allergic contact dermatitis
    - Psoriasis
    - Cutaneous Lupus
    - Pemphigus
  - *Interleukin-2*
    - Vitiligo
    - Pemphigus
    - Dermatomyositis
    - Psoriasis
- Rare neutrophilic dermatoses and necrotizing vasculitis.



# References

1. Drug Eruptions – Uptodate.com
  - [http://www.uptodate.com.proxy.pnwu.org/contents/drug-eruptions?source=see\\_link#H15](http://www.uptodate.com.proxy.pnwu.org/contents/drug-eruptions?source=see_link#H15)
2. DermIS.Net
3. NEJM
  - Roujeau JC, Stern RS. Severe Adverse Cutaneous Reactions to Drugs. *NEJM*. 1994; 331: 1272-85.
4. Frontiers of Public Health
  - Rubinstein E, Keynan Y. Vancomycin revisited – 60 Years Later. *Front. Pub. Health*. 2014; 2: 1-7.