**Objectives**

- Participants will:
  1. Describe impact of pharmacological therapy on wound healing and wound generation.
  2. Describe categories and patho-mechanisms of drug-induced skin reactions.
  3. Delineate drugs that commonly and rarely cause drug-induced skin reactions.
  4. Explain presentation and therapy of exemplar drug-induced skin reactions.

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**Normal Wound Healing**

- Human body “wired” to heal
- Despite any obstacles, most wounds heal
- Not here to discuss this comforting reality
- Here to discuss pharmacologic impact on wound healing and wound generation

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**Stages of Wound Healing**

- **Hemostasis (Injury)**
  - Vascular constriction
  - Platelet activation
  - Blood clotting cascade (PDGF, TGF-B, TGF-A, EGF)

- **Inflammation**
  - Cell recruitment (neutrophil, monocyte, lymphocytes, macrophage)
  - Phagocytosis
  - Debridement (PDGF, TGF-B, TGF-A, IL-2, IFN, EGF, TNF-A)

- **Proliferation**
  - Release of cytokines
  - Cell growth and activation (epithelial cells, fibroblasts, endothelial cells)
  - Neovascularization (angiogenesis)
  - Granulation tissue formation (PGDF, TGF-B, PDGF, IFN, TGF-A, EGF)

- **Maturation**
  - Wound contraction
  - Fibroblasts, epithelial cells
  - Vascular maturation and retraction
  - Remodeling (TNF-A, IL-1, PDGF, TGF-B, EGF)

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**Chronic Wound**

(Armstrong & Meyr, UptoDate, 2015)

- Defined as wound that is physiologically impaired due to:
  - Inadequate angiogenesis
  - Impaired innervation
  - Impaired cellular migration
- Medications can affect any aspect
Major Topics

- Drugs and Wound Healing: Drugs Helping and Drugs Hindering Healing
- Categories/classifications of drug-induced skin reactions
- Common and uncommon drug offenders
- Exemplar disorders
  - Exanthems
  - Blistering Response
  - Immune-mediated (SJS/TEN)
  - Hematologic – WISN, HIT Syndrome Necrosis

Scope of Medication Impact

- Wound healing affected by many drugs and disease processes
- Nearly 50% of Americans take one prescription drug monthly
- Twenty percent take three drugs or more a month
- Eleven percent take five or more drugs (CDC, 2015)

Medications Associated with Wound Healing Delays

- Anticoagulants
- Antimicrobials
- Aspirin/NSAIDs
  - NSAIDS impair fibroblasts, weaken wound contraction with long-term use (Guo et al, 2010)
- Povidone/Iodine
- Colchicine
- Dakin’s solution
- Glucocorticoids
- Immunosuppressive agents
- Anti-angiogenesis agents

Medications Hindering Wound Healing

- Antineoplastic agents
  - Reduce RBC and WBC presence
  - Damage keratinocytes
  - May decrease angiogenesis by decreasing VEGF
- Colchicine
  - Reduces granulocyte migration
  - Reduces fibroblast synthesis
- Vasoconstrictors
  - Decrease tissue perfusion
- Anti-rheumatoid drugs
  - Methotrexate: cytotoxic to T cells and macrophages
- Nicotine and smoking (but NRT does not impair wound healing)

Cancer Chemotherapy: Antiangiogenics (Choueiri & Sonpavde, 2015)

- Use is expanding
  - Bevacizumab (Monoclonal antibody; VEGF inhibitor)
  - Afibercept (VEGF ligand inhibitor)
  - Sunitinib (Tyrosine kinase inhibitor)
- Can cause impaired wound healing, osteoradionecrosis of jaw, hand-foot skin reaction

Steroids

- Notorious inhibitors of wound healing
- Notorious for systemic effects (hyperglycemia, osteoporosis, mood changes)
- Steroids affect cells by altering gene expression after crossing cell membrane
- Consequently affect almost every phase of wound healing
- Degree of inhibition related to potency of steroid
Steroids: Specific Effects

- Delay in removal of bacteria and foreign bodies
  - Decreased neutrophil and macrophage activity
- Decrease in epithelial regeneration and granulation activity (caused by steroids anti-mitotic activity)
- Decrease in fibroblast activity
- Over time thinned epidermis inhibits wound contraction
- Yet no problem with acute surgical healing if not long-term use (Treadwell, 2013; Wang et al, 2013)
  And when used topically may help healing

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

- Work by inhibiting Cyclooxygenase (COX)
- NSAIDs – have well known effect on delaying bone healing
- Krischak et al (2007): Found diclofenac inhibited fibroblasts after use in 10 rats (lab testing)
- Can affect ligament health too

Other Side Of The Coin

Other medications and treatments that can improve wound healing include:

- Hemorrhheologics (e.g., pentoxifylline (Trental))
- Hormones (estrogen)
- Phenytoin (think gums)
- Prostaglandins
- Zinc
- Vitamins A and C

Medications Improving Wound Healing

- Topical "Natural" Medications
  - Aloe vera
  - Curcumin
  - Ginger
  - Medicinal Honey
- Off Label Topical Drugs
  - Calcium Channel Blockers
  - Topical Regular Insulin
  - Topical Nitroglycerin
  - Topical Dilantin

When Drugs Cause Wounds (Skin Damage)

- Topical "Natural" Medications
  - Aloe vera
  - Curcumin
  - Ginger
  - Medicinal Honey
- Off Label Topical Drugs
  - Calcium Channel Blockers
  - Topical Regular Insulin
  - Topical Nitroglycerin
  - Topical Dilantin
Cutaneous Drug Reactions

- One of most common adverse reactions
- Overall incidence rate of 2−3% in hospitalized patients
- Almost any medication can induce skin reactions
- Selected drug classes have rates as high as 5% (Lee & Thomson)
- Some reactions are immunological; most are not (thankfully)

Type A/Type B Categories

Type A: 85−90% of adverse drug reactions (ADEs); predictable from known pharmacologic properties of a drug. Examples:
- Diarrhea – Antibiotics
- Gastritis – NSAIDs
- Kidney toxicity – Aminoglycosides (Kaniwa et al, 2013)

Type B: 10−15% of ADEs hypersensitivity: Immunologic or other patho-mechanisms; have signs/symptoms different from action of drug usually not predictable.
Examples: Exaggerated sensitivity to known drug reactions – tinnitus from low dose aspirin (Kaniwa et al, 2013)

Immunological (Hypersensitivity) Reactions

Type I: Caused by drug/antigen specific IgE that links with mast cells and basophils – immediate release of histamine/leukotrienes get urticaria, angioedema, anaphylaxis (aspirin, penicillins)
Type II: Cytotoxic reactions based on IgG or IgM – mediated mechanisms antibody ruptures cell (blood cell dyscrasias like hemolytic anemia and thrombocytopenia)
Type III: Mediated by intravascular immune complexes. Antibodies and drug antigens in circulation. Phagocytes remove complexes and ends up in skin, kidneys, etc. (serum sickness, vasculitis)
Type IV: Mediated by T cells; cause “delayed” hypersensitivity (contact dermatitis, SJS and TENS)

Uncommon Drug Offenders (Rarely Cause Skin Eruptions)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>Muscle Relaxants</td>
</tr>
<tr>
<td>Antihistamines (oral)</td>
<td>Nitrates</td>
</tr>
<tr>
<td>Atropine</td>
<td>Nystatin</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Oral Contraceptives</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Propanolol</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Insulin</td>
<td>Thyroid Hormones</td>
</tr>
<tr>
<td>Laxatives</td>
<td>Vitamins</td>
</tr>
<tr>
<td>Local Anesthetics</td>
<td></td>
</tr>
</tbody>
</table>
Common Drug Offenders: Exanthems
- Allopurinol
- Antimicrobials (PCN, Cephalosporins, Erythromycin, Gentamicin, Anti-TB Drugs, Nitrofurantoin, Sulfadiazine)
- Barbiturates
- Captopril
- Carbamazepine
- Furosemide
- Gold Salts
- Lithium
- Phenothiazine
- Phenytoin
- Thiazides

Common Drug Offenders (Fixed Drug Eruption – Same Site)
- ACE Inhibitors
- Allopurinol
- Antimicrobials (Sulfa, Tetracyclines, Cephalosporins, PCN, Clindamycin, Trimethoprim, metronidazole)
- Barbiturates
- Benzodiazepines
- Calcium Channel Blockers
- Carbamazepine
- Flucloxacillin
- Lamotrigine
- NSAIDs
- Paclitaxel
- Proton Pump Inhibitors (Omeprazole, Lansoprazole)
- Salicylates
- Terbinafine

Common Drug Offenders Urticaria (Angioedema)
- Antibiotics (PCN, Cephalosporins, Sulfa, Tetracyclines)
- Anti-epileptics
- Codeine and Opioids
- Aspirin, ACE-I, NSAIDs
- PCN, Sulfa, ASA, Cholecystographic Dyes
- Benzoic Acid, Sulphites, Aspartame

Common Drug Offenders Causing Psoriasisiform Eruptions
- ACE-I
- Beta Blockers
- Chloroquine
- Digoxin
- Gold
- Interferons
- Lithium
- NSAIDs
- Terbinafine
- Tetracyclines
- TNF–Alpha Antagonists

Common Drug Offenders (Vasculitis Reactions)
- Allopurinol
- Aspirin
- Beta-Lactam Antibiotics
- Carbamazepine
- Co-trimoxazole
- Dilazepam
- Erythromycin
- Furosemide
- Gold
- Hydralazine
- Methotrexate
- NSAIDs
- PTU
- Sulfasalazine
- Sulfonamides
- Thiazides
- Thrombolytic Agents

Comparing Drug Reactions (Cooper, 2012)

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Allergic Reaction</th>
<th>SJS</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Low grade</td>
<td>Possible</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin eruption</td>
<td>Central rash, no</td>
<td>Macules or blisters progressing to detachment of epidermis, rash may begin on face, trunk; spread to limbs; macules may be painful</td>
<td>Same as SJS</td>
</tr>
<tr>
<td>SOB/wheezing</td>
<td>Early</td>
<td>Late due to lesions in resp. tract</td>
<td>No</td>
</tr>
<tr>
<td>Swelling face, tongue</td>
<td>Early</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Runny nose, itchy eyes</td>
<td>Early</td>
<td>No</td>
<td>Late</td>
</tr>
<tr>
<td>Myalgia, joint pain</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Common Drug Offenders (SJS/TEN)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SJS/TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins*</td>
<td></td>
</tr>
<tr>
<td>Beta-Lactams</td>
<td>Anti-TB Drugs</td>
</tr>
<tr>
<td>Carbamazepine*</td>
<td>Barbiturates*</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>Carbamazepine*</td>
</tr>
<tr>
<td>Co-Triamterene</td>
<td>Gold*</td>
</tr>
<tr>
<td>Co*</td>
<td></td>
</tr>
<tr>
<td>Co-Antagonists</td>
<td>Lamotrigine*</td>
</tr>
<tr>
<td>Lamotrigine*</td>
<td>Lamotrigine*</td>
</tr>
<tr>
<td>Sulfasalazine*</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>Mefloquine</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Mefloquine</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Penicillins</td>
</tr>
<tr>
<td>Penicillins*</td>
<td>Phenoxazin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Saliacylates</td>
</tr>
<tr>
<td>Sulfonamides*</td>
<td>Sulfonamides*</td>
</tr>
<tr>
<td>Tetracyclines*</td>
<td>Tetracyclines*</td>
</tr>
<tr>
<td>Thiazides</td>
<td></td>
</tr>
</tbody>
</table>

* Can cause SJS and TEN

Exemplar Drug–Induced Reactions

- Exanthems
- Blistering Reactions
- Immune Mediated (SJS and TEN)
- Hematologic (WISN and HIT Syndrome Necrosis)

Exanthems

- Umbrella term for skin reaction that “bursts forth” characterized by:
  - Erythema (Redness)
  - Morbilliform (Resembling Measles)
  - Maculopapular (Most common exanthem) (Commonly caused by PCNs and Sulfonamides)
  - Account for 90% of all drug rashes (Bircher, 2014; Samuel & Chu, 2014)

Blistering Reactions

- Idiopathic pemphigus and bullous pemphigoid are examples
- Erythema, crusting, scaling are common
- Can get large tense blisters on red base
- Usually benefits from cessation of causative agent

Bullous Pemphigoid
Immune-Mediated ADR: SJS and TEN

- Codified by percentage of skin detachment (Clinard et al, 2012)
- SJS and TEN represents variants on spectrum of disease
- **SJS**: Fever, malaise, myalgia, and skin eruptions (<10% of body) (blisters, papules, erythematous areas); usually involves mucosa (eyes, genitals, mouth)

Immune-Mediated ADR: SJS and TEN

- **TEN**: full thickness epidermal necrosis; get fever, malaise, nausea, vomiting, myalgia, arthralgia, and skin changes (>30% of body affected); erythema, bullae; skin detaches in sheets; mucosa is also involved

### SJS

![SJS Image]

### TEN

![TEN Image]

### Hematologic Dermatologic ADR

- **WISN**: Warfarin–induced skin necrosis(aka coumadin necrosis)
- **WISN**: occurs 3 to 5 days after dose of warfarin; often in patient with Protein C and Protein S deficiencies
  - Red painful plaques
  - Progress possibly to hemorrhagic blisters, ulcers, necrosis (Clinard et al)
- **WISN Risk Factors**: female gender, obese body type, middle age, inpatient hospital stay; anticoagulation for DVT, prosthetic cardiac valve surgery, high coumadin loading doses
- Coumadin introduced in 1940s so condition has been “around” for decades

### Warfarin Necrosis

![Warfarin Necrosis Image]
Drugs Induced Cutaneous Reactions

WHAT TO DO??

Hematologic ADR of Skin

- HIT Syndrome (Specifically HIT II)
- Type I: transient platelet decrease: Type II: Immune-mediated antibody formation
  - Get loss of heparin due to Immune complex (HIT antibodies)
  - Get destruction of platelets from antibody complexes (Trautman et al, 2010)
  - Decreased platelets < 150,000
  - Get arterial and venous thrombosis
  - Necrosis of skin in fatty areas as abdomen, thighs – can also be blisters, purpura
  - Diagnosis: Use ‘4Ts Score’ (Thrombocytopenia, timing of platelet fall, thrombosis and sequelae, other causes for thrombocytopenia) (Coutre, 2015)

WHAT TO DO??

- Drug withdrawal
- Symptomatic therapy:
  - Diphenhydramine 25–50mg orally every 4–6 hours (adults > 12 years) Use till pruritus subsides
  - Hydroxyzine – 25mg orally TD to QID (Adults)
  - Cetirizine – 10mg orally daily (Adults)
  - Short course of moderate does steroids (prednisone 1–2mg/kg/day) (only if rash more severe) (Bircher, 2014)

Pharmacological Management: Exanthems

- Drug withdrawal
- Symptomatic therapy:
Pharmacologic Management: Blistering Reactions (e.g., Pemphigoid like lesions)

- Discontinue offending drug
- Oral corticosteroids have been mainstay of treatment (Kirtschig et al, 2013)
  - Usually moderate dose

Immune-Mediated Conditions: SJS and TEN

- Discontinue triggering drug immediately (most frequently, sulfonamides, PCNs, Cephalosporins, Fluoroquinolones)
- Transfer to Burn Center for SJS/TEN
- Treatment of skin lesions – topical therapy with antimicrobials (silver in variety of forms)
- Fluids and nutrition
- Treatment with systemic corticosteroids is controversial (some say good; others ineffective) (Gerull et al, 2011) - Tendency to avoid steroids (Mockenhaupt et al, 2002)
- New trials with IV immune globulin show some positive impact on prognosis but also are conflicting (High et al, 2014)

Pharmacologic Management: Hematologic Skin Reactions

Warfarin–Induced Skin Necrosis

- Mainstay of therapy is supportive
- Discontinue warfarin immediately
- Need another anti-coagulant – usually low molecular weight heparin (if no heparin allergy)
- Other newer anticoagulants are possible too (Kozac et al, 2013)

HIT Syndrome

- Cessation of heparin immediately (in all exposures)
- Avoidance of any heparin–based products (UFH and LMWH)
- Switch to alternative anticoagulants
  - Argatroban (direct thrombin inhibitor)
  - Danaparoids
  - Eventually switch to coumadin or other agent
- Established process
  - For Prevention: Use LMWH, Heparin analogues (Fondaparinux) and see much lower rates of HIT

General Management Points for Drug–Related Eruptions

- Take detailed accurate medication history
- Note use of all OTC medications as well (St. John’s Wort, Echinacea)
- Note injections – including vaccines or contrast media
- Note time of medication relative to onset of reaction
- Take detailed medical history: Any history of drug sensitivity, contact dermatitis, connective tissue disease, atopy (asthma, eczema)

General Management Points

- Examine skin eruption closely and determine if drug–related
- Educate patient about avoidance of drug in future; record clearly in history
- Notify pertinent regulatory authorities
Summary

- Discussed drugs and wound healing
- Discussed uncommon and common offenders for adverse drug reactions of skin
- Discussed several possible presentations
- Explained pharmacotherapy for exemplar disorders

References


References


References

## References