# NJHA Pressure Injury Prevention Conference
# Pharmacologic Impacts on Wound Healing: When Drugs "Break Bad"

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# Objectives

Participants will:

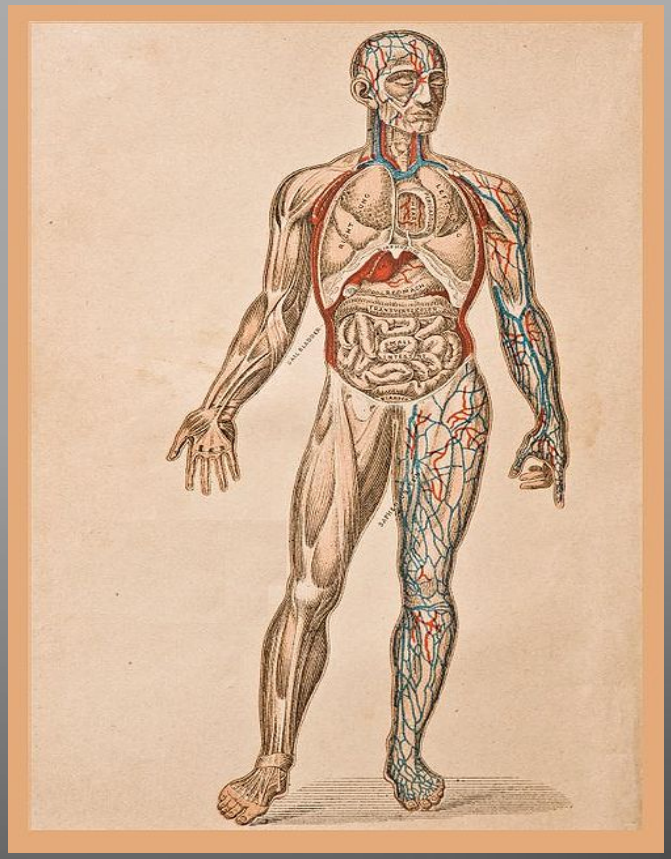
1) Identify common conditions associated with non-wound-related polypharmacy.
2) Determine data for drugs that impair wound healing processes.
3) Recognize drugs that may contribute to wound healing.
4) Explain drugs that may cause wound reactions.
5) Describe clinical practices mitigating drug effects

# Major Topics

- Normal wound healing processes
- Chronic disease prevalence and wounds
- Drugs and wound healing/wound healing Impairment
- Common and uncommon drug offenders
- Clinical implications for wound professionals

# Normal Wound Healing

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



# Normal Wound Healing

- Four phases overlapping/special cells (keratinocytes, fibroblasts, endothelial cells, macrophages, platelets)
- **Hemostasis** – platelets, growth factors (immediate)
- **Inflammation** – macrophages, leukocytes, mast cells (day 1–4)
- **Proliferation** – fibroblasts, myofibroblasts, endothelial cells
- **Remodeling** (maturation) (Day 21 – 2 years) (80% of original strength)

# 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, FGF, IGF, IFN, TGF-A, EGF)

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

# Chronic Wound (Armstrong & Meyr, UptoDate, 2017)

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

# Scope of Chronic Disease in United States: Mortality and Morbidity

- In 2015, top 10 leading causes of death accounted for approximately 75% of all US deaths
- In 2015, 2,712,630 Americans died (86,212 more than 2014) (CDC, 2017)

# Top 10 Causes of Death

1) Heart Disease*
2) Cancer*
3) Chronic Lower Respiratory Disease*
4) Unintentional injuries
5) Stroke*
6) Alzheimer's Disease*
7) Diabetes*
8) Influenza/pneumonia
9) Kidney Disease*
10) Suicide

*Chronic Disorders

(CDC, 2017)

# Chronic Diseases in USA

- As of 2012, half of all American adults had one or more chronic diseases
- Constitutes 117 million Americans
- Obesity – serious health disorder – approaching 50% are obese or overweight
- Diabetes mellitus type 2 – pandemic
- Risk behaviors: Little or no exercise, poor dietary habits (fat, calories, salt), smoking (1 in 5 adults), alcohol abuse (CDC, 2017)
- Arthritis affects 53 million Americans

# Chronic Diseases in USA

- 86% of all US healthcare spending in 2010 was for people with one or more chronic diseases
- In Americans over 65, 3 of 4 have multiple chronic conditions.
- 93% of total Medicare spending in 2012 was for people with multiple chronic conditions (CDC, 2017; CMS, 2012)

# Chronic Wounds

- Pressure injuries – focus of today's conference
- Venous ulcers
- Arterial ulcers
- Neuropathic (diabetic) ulcers
- Vasculitic and "other" ulcers
- Just about ALL wound patients are receiving medication therapy

# 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, 2017)
- Thirty-six million Americans use herbals yearly (Ranade & Collins, 2014)
- U.S. herbal use grew for 12th straight year (Crane, 2016)

# Critical Nexus: CI and Polypharmacy


# 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
  - Useful and safe if used diluted and for short-term
- Glucocorticoids
- Immunosuppressive agents
- Anti-angiogenesis agents

# Medications Hindering Wound Healing

- Antineoplastic agents
  - Reduce RBC and WBC presence
  - Damage keratinocyte
  - May decrease VEGF and angiogenesis
- 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 healing)

# DMARDS and SSI/Delayed Wound Healing

- Kaduta et al (2015) retrospective record review of 1036 elective orthopedic surgery patients
- Looked at risk factors for SSI and DWH
- Risk factors were foot/ankle surgery, total knee arthroplasty, and rheumatoid arthritis (RA) disease duration
- Looked at conventional synthetic DMARDs; looked at biologic DMARDs as variables
- Neither were risk factors
- Why?? – drugs **stopped** 2-4 weeks before surgery
- Restarted infliximab in 4 weeks after surgery; others (Entanercept, Adalimumab, Tocilizumab, Golimumab) restarted after healing of surgical wounds

# DMARDs and Wound Healing: Case Study

- Gaucher et al, 2017
- 53-year-old male with sarcoidosis and steroid-induced diabetes
- Receiving methotrexate and prednisone
- Developed LLE cellulitis
- Stopped prednisone
- Treated cellulitis
- Four rounds of skin grafting: stopped methotrexate
- Fifth skin graft was successful

# Cancer Chemotherapy: Antiangiogenics (Choueiri & Sonpavde, 2017; McIntyre, 2015)

- Use is expanding
  - Bevacizumab (Monoclonal antibody; VEGF-A inhibitor)
  - Aflibercept (VEGF-A, VEGF-B)
  - Sunitinib (Tyrosine kinase inhibitor)
- Can cause impaired wound healing, osteo-necrosis of jaw, hand-foot skin reaction, hand-foot syndrome, and bleeding

# 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
- **Long-term** usage impact is the challenge: bottom line is immune modulation (and associated derived risks)

# 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 (e.g., stasis dermatitis)

# Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

- Work by inhibiting Cyclooxygenase (COX)
- COX affects arachidonic acid and prostaglandins; blocking has serious effects
- 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

# NSAIDs and Long Bone Fracture Healing (Jeffcoach et al, 2014)

- Retrospective study of all orthopedic patients with femur, tibia, and/or humerus fractures between October 2009 and September 2011 – University of Tennessee Level 1 Trauma Center
- 1,901 patients with LBFs
- Assessed for complications: Nonunion/malunion, infection
- 60 patients had complications
- Logistic regression calculated ORs
- Patient more likely to have complication if received NSAIDs postop (OR 2.17) or if they were smokers (OR 3.19)
- Recommend **avoidance of NSAID** use in traumatic LBF

# NSAID Use and Postoperative Gastrointestinal Surgery

- Large retrospective study of adult GI surgery patients between 2008 and 2012
- Among 398,752 patients, 55% underwent colorectal surgery and 45% had non-colorectal GI surgery.
- Five percent of all received ketorolac (IV)
- These patients had higher odds of re-intervention (OR 1.20), emergency room visit (OR 1.44) and 30-day readmission (OR 1.11) and readmission for anastomotic complications (OR 1.2)
- Use great caution when using IV ketorolac in patients undergoing GI surgery

# Animal Studies Give Some Insights: Arslantas (2015)

- Tested 42 rats with **oral** sildenafil (10mg/kg) in 1cc distilled water via NG tube vs. sodium chloride injection in intraperitoneum (21 exp; 21 control)
- Created an ischemic skin wound on rats' abdomens
- Checked healing at days 3,5,10 on 7 rats in each group
- Theoretically sildenafil (PDE-5 inhibitor) should help healing
- Sildenafil significantly reduced re-epithelialization, neovascularization, granulation tissue and number of inflammatory cells on day 3
- *Increased* inflammatory cells on day 10
- Oral vs. Topical sildenafil: have differential effects on wounds

# Other Side Of The Coin

# Medications *Improving* Wound Healing

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

# Medications *Improving* Wound Healing

- Topical "Natural" Medications
  - Aloe vera
  - Curcumin
  - Ginger
  - Medicinal Honey
  - Mucilage (in Slippery Elm)
  - Witch Hazel
- ***Off Label*** Topical Drugs (in the literature)
  - Calcium Channel Blockers
  - Topical Regular Insulin
  - Topical Nitroglycerin
  - Topical Dilantin

# Clinical Wake Up Call

- Polypharmacy is the norm
- Co-morbidities are common
- Drugs involved in all wound patients care

# Case Study From Real World

- 94-year-old female admitted from home; cared for by son who is devoted to her; sits at bedside; multiple co-morbidities including dementia, poor nutrition, immobility and frailty
- Consultation for wound care team: has pressure injuries on sacrum, bilateral hips and sternum
- Also has “rash” on extremities and trunk
- Multiple medications; nothing new except recently began Aricept (donepezil)

# When Drugs “Break Bad”

# Drugs Can CAUSE Wounds

# Cutaneous Adverse Drug Reactions

- One of most common adverse reactions
- Overall incidence rate of 2-3% in hospitalized patients
- Almost any (1:1000 hospitalized patients (Ijaz, 2015)) medication can induce skin reactions
- Selected drug classes have rates as high as 5% (Lee & Thomson)
- Some reactions are immunological; most are *not* (thankfully)
- Categorized by predictability (pharmacological) or immune basis

# 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 A/Type B Categories

**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**: Cased 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)

# Immunologic (Hypersensitivity) Reactions

**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)

| | |
|---|---|
| Antacids | Muscle Relaxants |
| Antihistamines (oral) | Nitrates |
| Atropine | Nystatin |
| Benzodiazepines | Oral Contraceptives |
| Corticosteroids | Propanolol |
| Digoxin | Spironolactone |
| Ferrous Sulfate | Theophylline |
| Insulin | Thyroid Hormones |
| Laxatives | Vitamins |
| Local Anesthetics | |

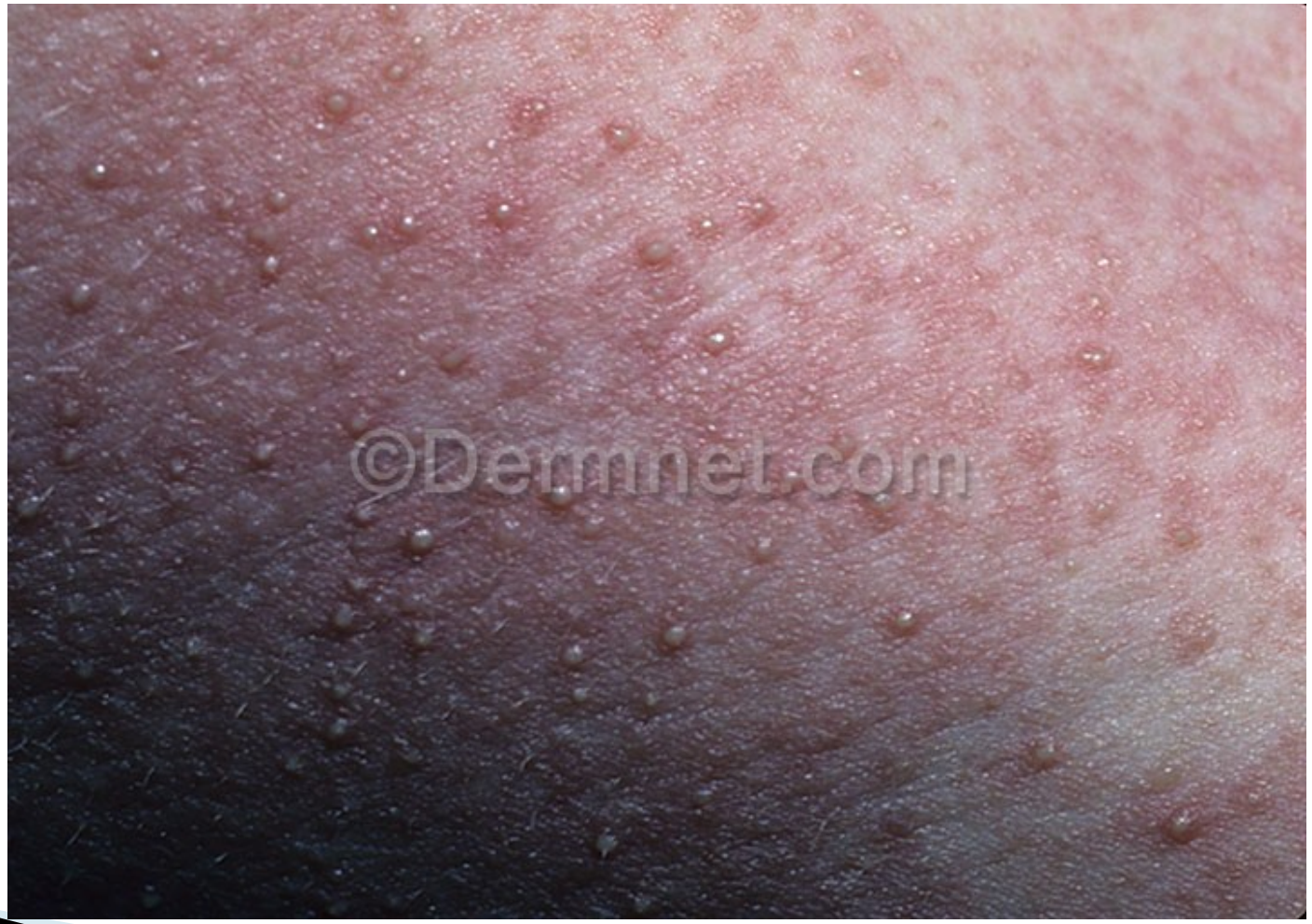
# Type of Skin ADEs

- Exanthems
- Fixed Drug Eruptions (Allergic)
- Blistering
- Psoriasisiform
- Immune Mediated (SJS and TEN)
- Hematologic/Vasculitic

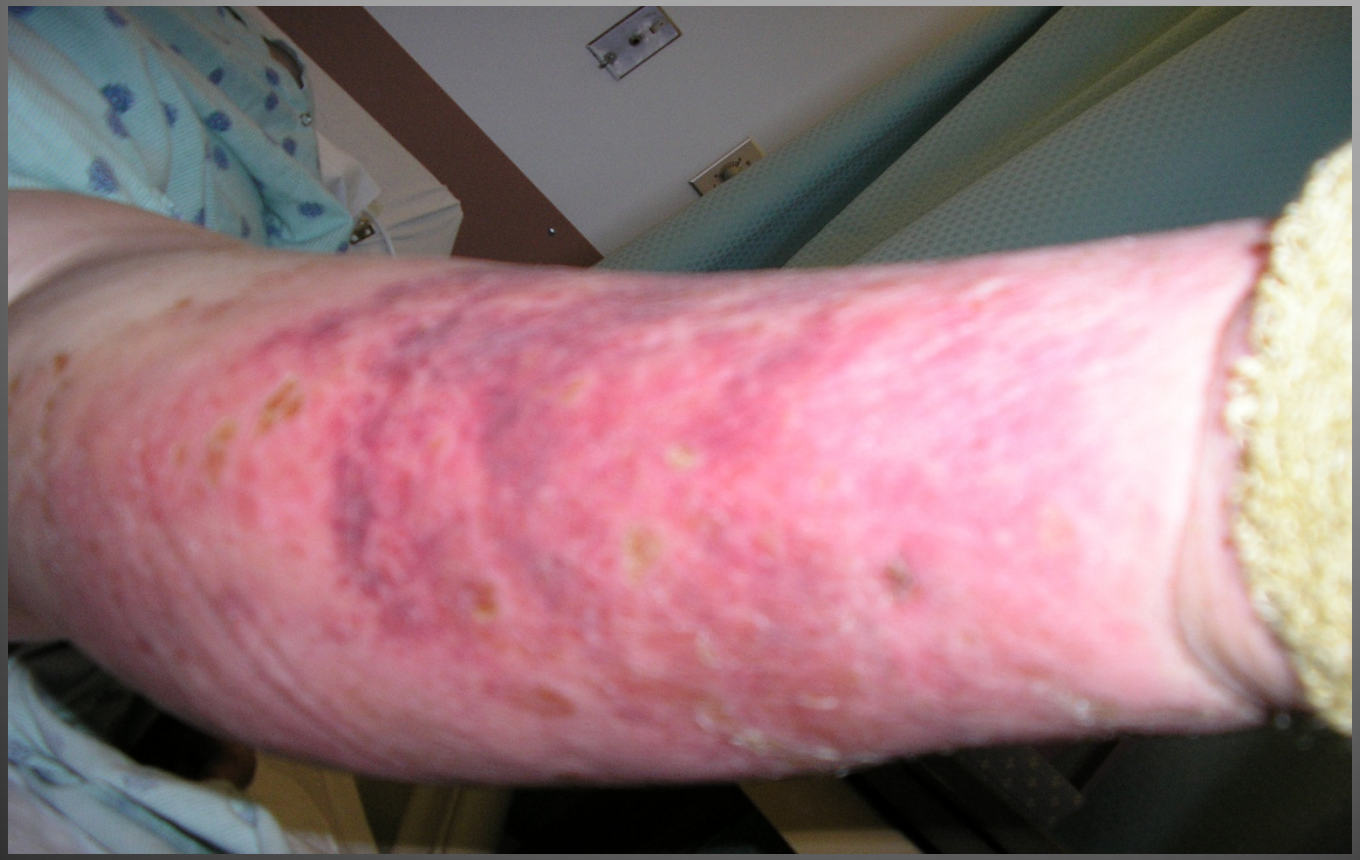
# Risk Factors for Skin ADE

- History of atopy
- Viral infections (e.g., HIV, Hepatitis C)
- Female gender
- Genetic polymorphism
- Connective tissue disorders
- Solid organ cancers (Ijaz, 2015)

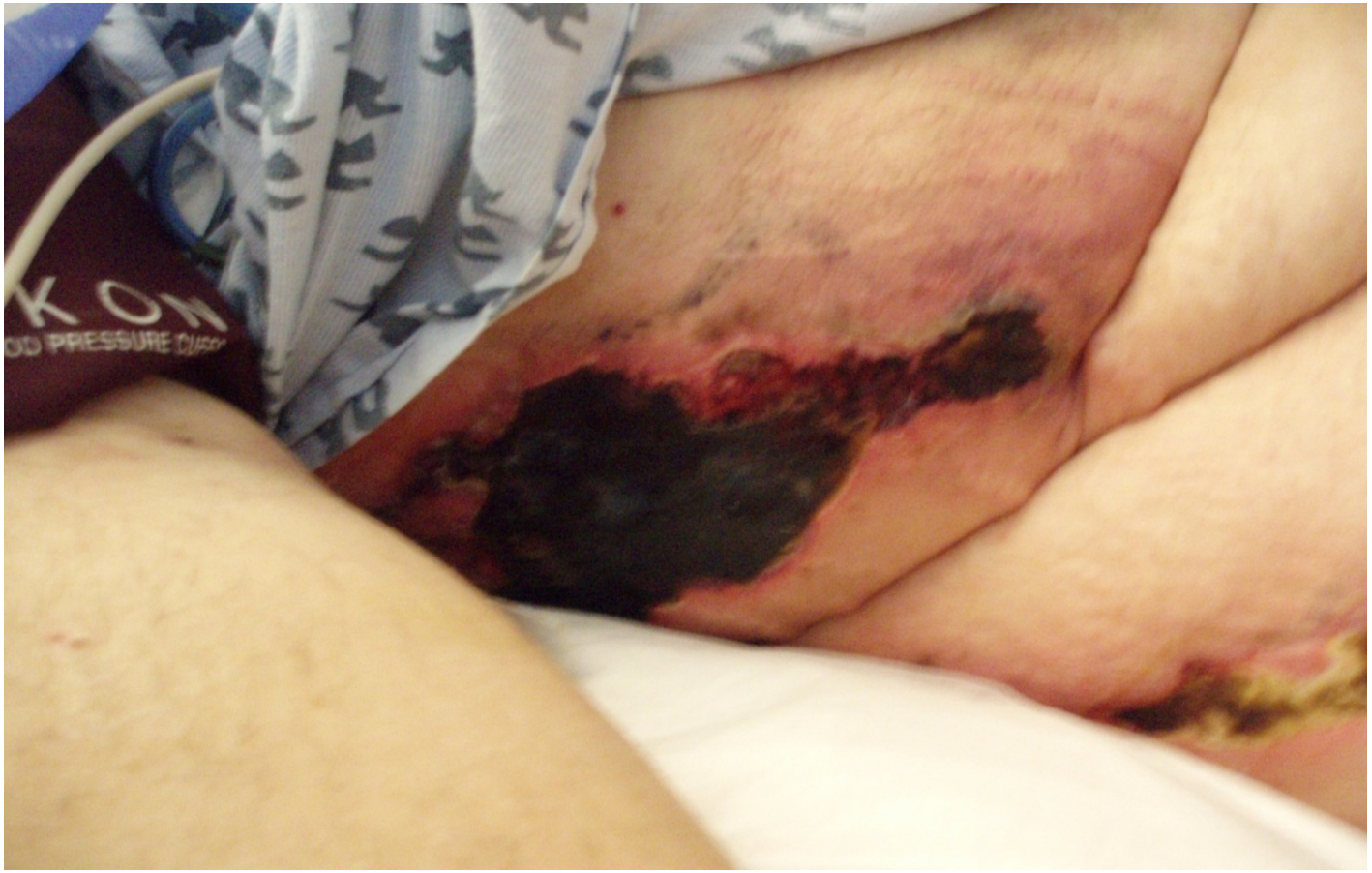
# Exanthem Response



# Blistering: Bullous Pemphigoid



# Hematologic: Warfarin Necrosis



# Common Drug Offenders: Exanthems

- Allopurinol
- Antimicrobials (PCN, Cephalosporins, Erythromycin, Gentamicin, Anti-TB Drugs, Nitrofurantoin, Sulfa)
- 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
- Fluconazole
- Lamotrigine
- NSAIDs
- Paclitaxel
- Proton Pump Inhibitors (Omeprazole, Lansoprazole)
- Salicylates
- Terbinafine
- *Reaction at same site or sites each time drug is taken

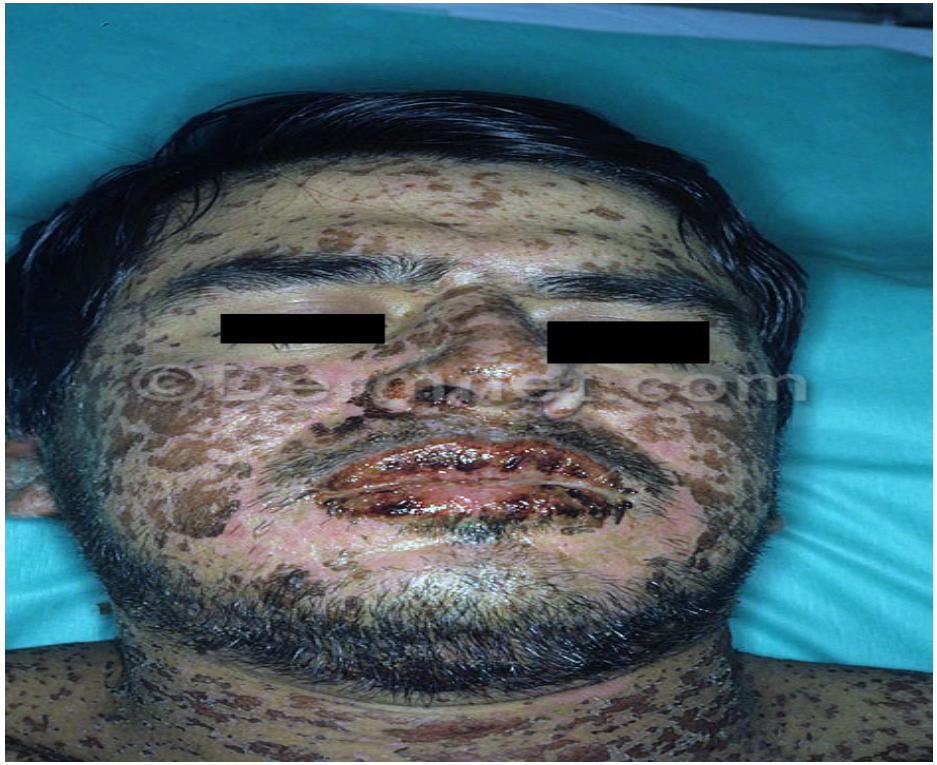
# Common Drug Offenders Blistering Reactions

- ACE Inhibitors (captopril, enalapril)
- antibiotics (cephalosporins, penicillins, sulfa agents, tetracyclines, vancomycin)
- gold/sodium aurothiolamar
- lithium
- loop diuretics (eg, furosemide, bumetanide)
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- penicillamine
- thiazide diuretics (eg, hydrochlorothiazide)

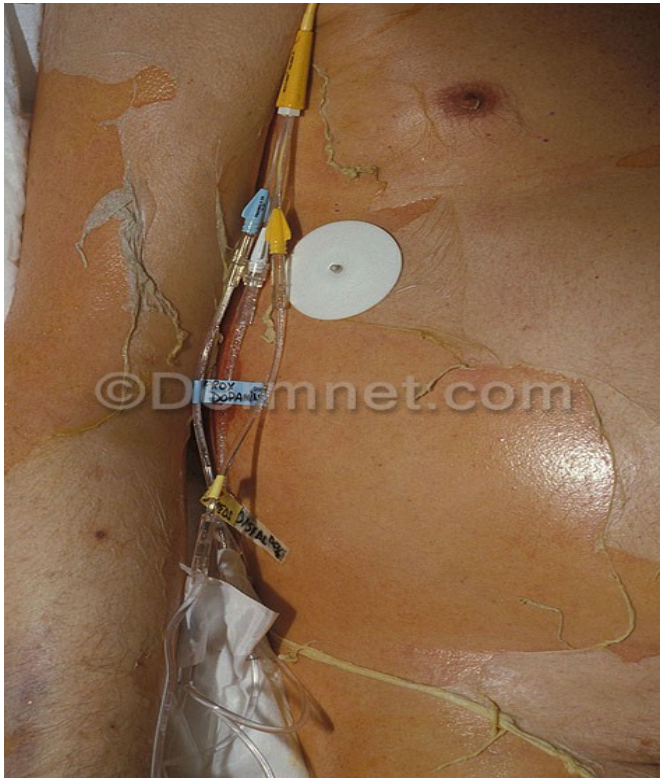
# Common Drug Offenders Causing Psoriasisiform Eruptions

- ACE-I
- Beta Blockers
- Chloroquine
- Digoxin
- Gold
- Interferons
- Lithium
- NSAIDs
- Terbinafine
- Tetracyclines
- TNF-Alpha Antagonists

# SJS



# TENS



# Common Drug Offenders (SJS/TEN)

| SJS | TEN |
|---|---|
| Barbiturates* | Allopurinol |
| Beta-Lactams | Anti-TB Drugs |
| Carbamazepine* | Barbiturates* |
| Chloropropamide | Carbamazepine* |
| Co-Trimoxazole | Gold* |
| Gold* | Griseofulvin |
| H2 Antagonists | Lamotrigine* |
| Lamotrigine* | Leflunomide* |
| Leflunomide* | |
| Macrolides | Nitrofurantoin |
| NSAIDs | NSAIDs* |
| Phenothiazines | Penicillins |
| Phenytoin* | Phenytoin* |
| Rifampicin | Salicylates |
| Sulfonamides* | Sulfonamides* |
| Tetracyclines* | Tetracyclines* |
| Thiazides | |

* Can cause both SJS and TEN

# Common Drug Offenders (Vasculitis Reactions)

- Allopurinol
- Aspirin
- Beta-Lactam Antibiotics
- Carbamazepine
- Co-trimoxazole
- Diltiazem
- Erythromycin
- Furosemide
- Gold
- Hydralazine
- Methotrexate
- NSAIDs
- PTU
- Sulfasalazine
- Sulfonamides
- Thiazides
- Thrombolytic Agents

# Clinical Implications for Wound Professionals

- Take detailed accurate medication history
- Note use of all OTC medications especially herbals
- Note injections – including vaccines or contrast media
- Note time of medication relative to onset of wound/skin problems (ADE)
- Take detailed medical history: Any history of drug sensitivity, contact dermatitis, connective tissue disease, atopy (asthma, eczema), previous wound healing delays

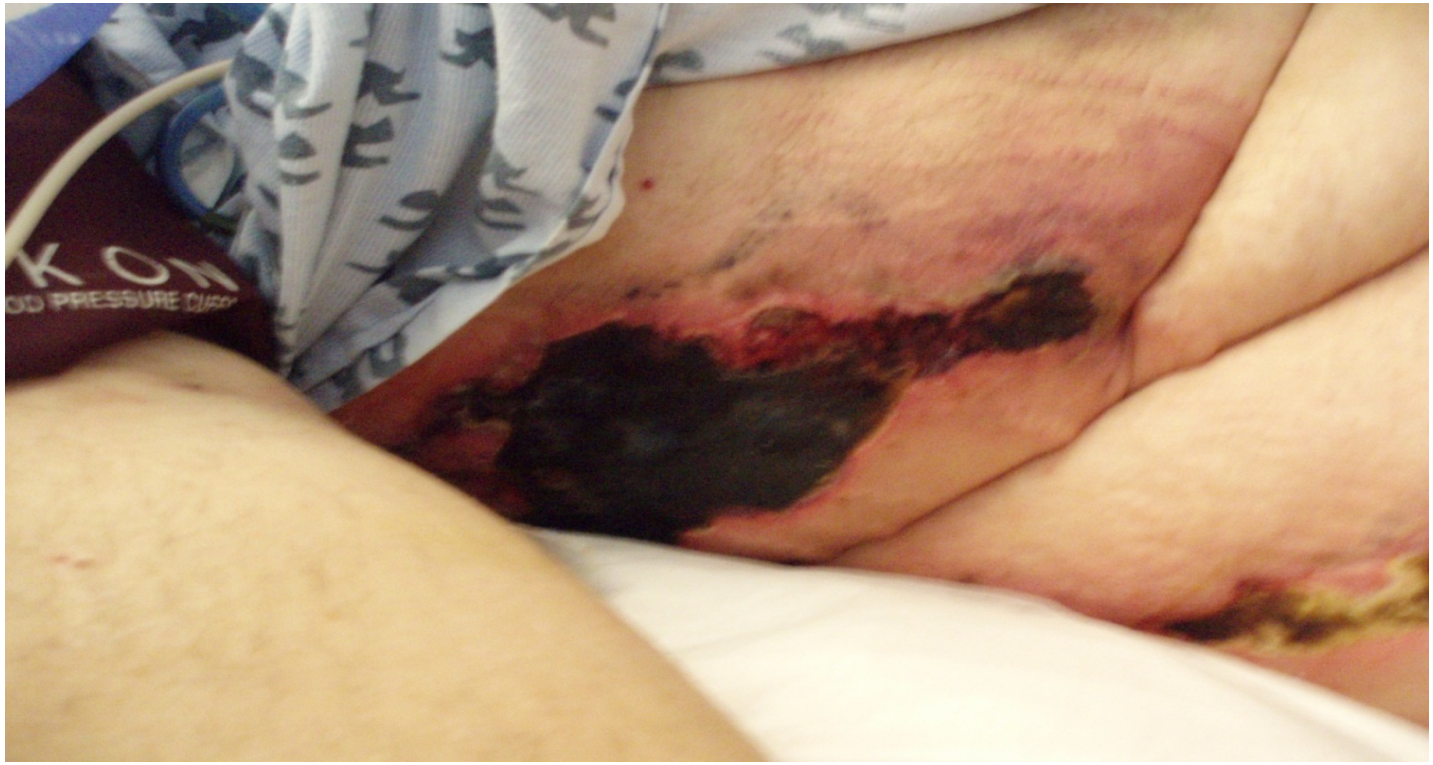
# General Management Points SKIN ADEs

- Examine skin eruption closely and determine if drug-related
- Educate patient about avoidance of drug in future; record clearly in history
- If serious enough, Medic Alert bracelet
- Notify pertinent regulatory authorities if serious reaction (FDA FAERS (Federal Adverse Event Reporting System: www.fda.gov)

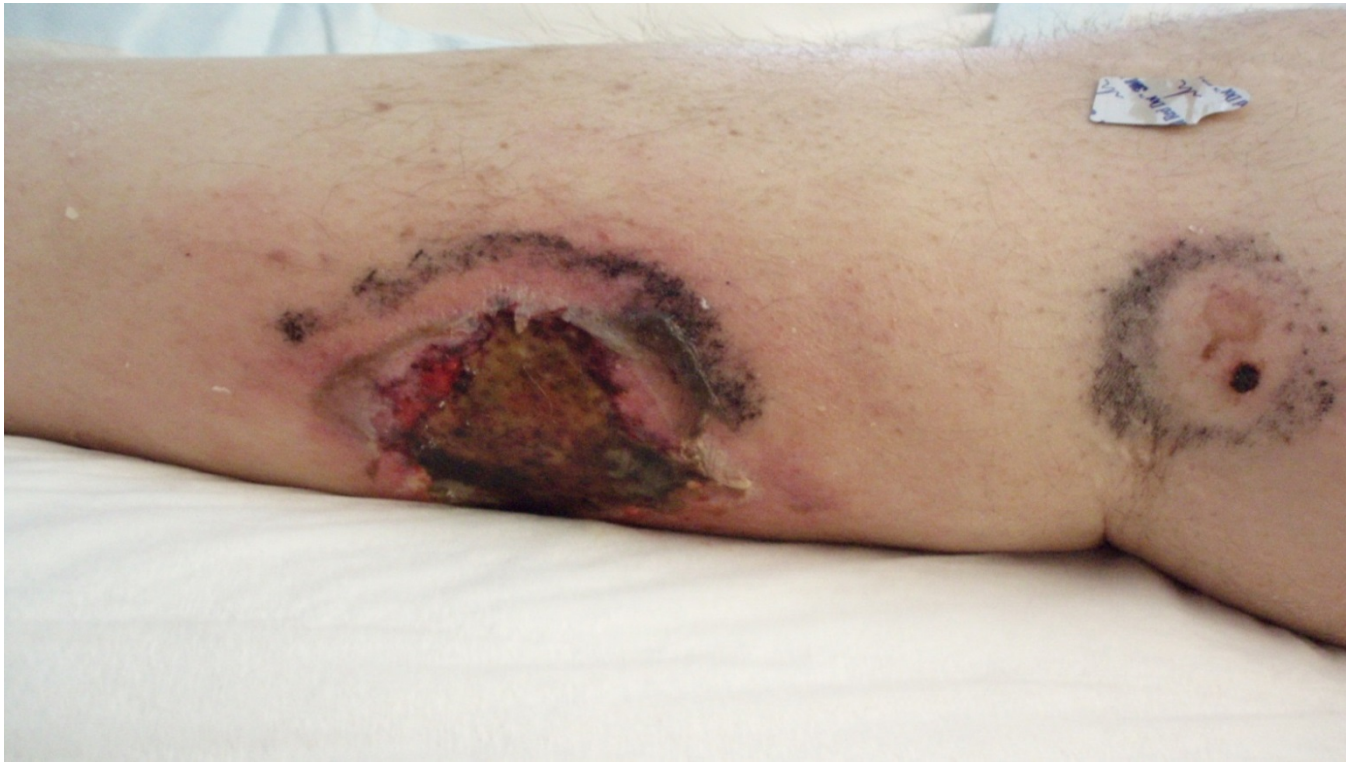
# Hematologic Dermatologic ADR

- WISN: Warfarin-induced skin necrosis
- HIT Syndrome
- WISN: occurs 3 to 5 days after dose of warfarin; often in patient with Protein C and Protein S deficiences
- Red painful plaques
- Progress possibly to hemorrhagic blisters, ulcers, necrosis (Clinard et al)

# Warfarin Necrosis



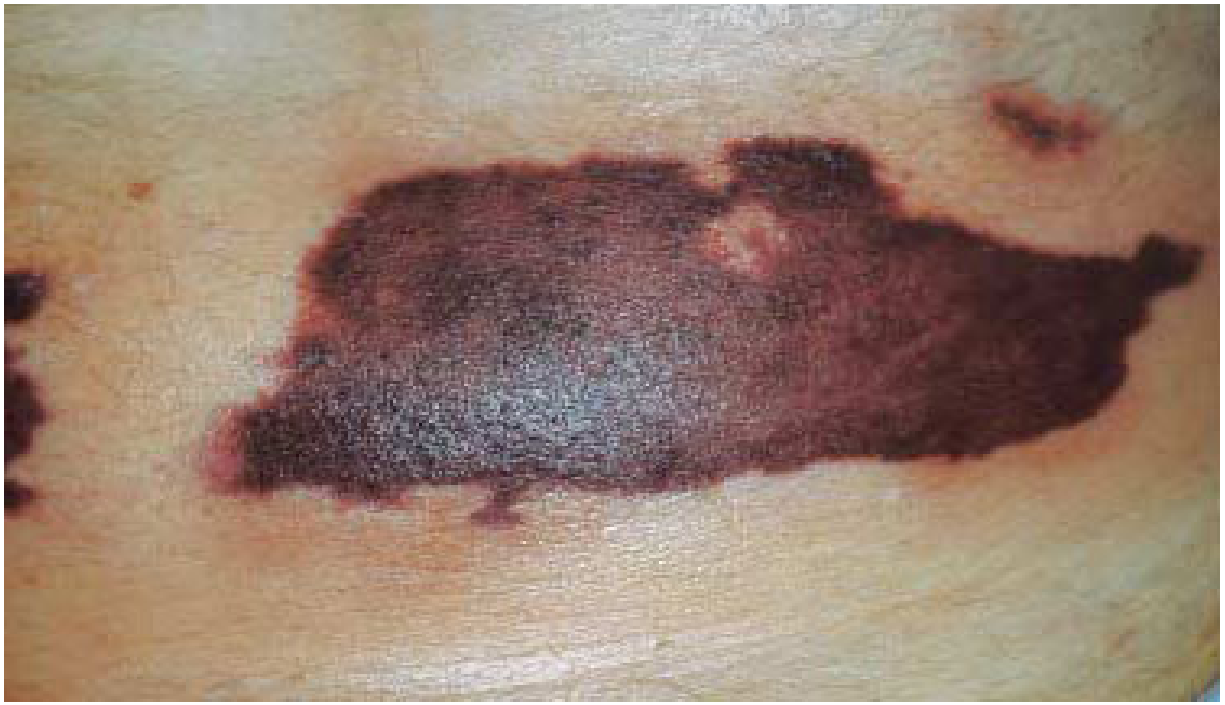
# Warfarin Necrosis



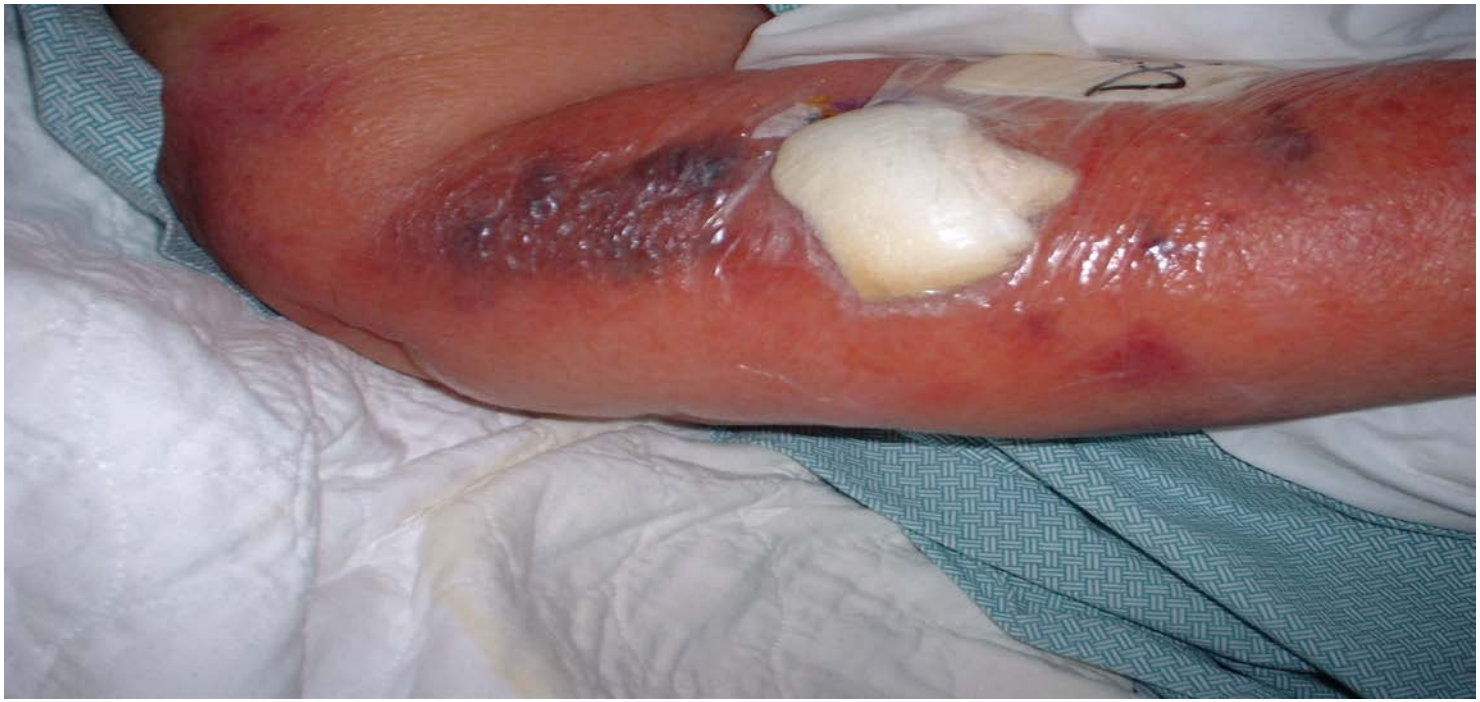
# Hematologic ADR of Skin

- HIT Syndrome (Specifically HIT II)
  - 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)

# HIT Skin Necrosis



# Heparin-Induced Thrombocytopenia Lesions



# Understanding Nature of ADEs

- Harkainen et al (2014) in a Finnish study of 463 patients looked at hospital records over 12 month time
- Total of 180 ADEs in 125 patients (27%)
- Of these 74(41%) were preventable; 95% caused temporary harm
- Most common ADE was abnormal blood potassium
- Risk was increased by duration of care and polypharmacy

# Addressing Wound Healing Inhibiting Factors

- Consider impact of **hidden malnutrition** (Protein insufficiency) on drug metabolism (protein binding and drug toxicities); does patient have fatigue, pain, mouth ulcers?
- Consider common drugs of **age groups** treated (in wound care and wound clinics mostly older)
  - Rheumatoid diseases and DMARDS (methotrexate and sulfasalazine etc.)
- Consider **polypharmacy** and need for "deprescribing"

# Addressing Other Wound Healing Inhibiting Factors

- Effects of **Aging** on Drug Metabolism and Excretion
  - With aging, liver function decreases by 40% so drugs can be "stored" and cause toxicity
  - Kidney function decreases with age; better to use creatinine clearance rather than creatinine level in elderly to monitor levels; affects drug excretion
  - Selected drugs with greater harm in elderly:
    - Antipsychotics (haloperidol)
    - Hypnotics (diazepam)
    - Diuretics (furosemide) (Kaufman, 2015)

# Addressing Other Wound Healing Inhibitors

- Usage of other “traditional” therapies
- 1) Need to ask if patient is consuming any herbal products (teas, liquid extracts, capsules)
- 2) Need to ask patient is applying any herbal topical preparation to wound
- 3) Potential for herbal-drug interaction: “Natural” does not mean safe
- 4) Does the patient space herbals away in time from other drugs (St. John’s Wort, Ginkgo biloba, etc.)

# Herbal Medicines and Wound Healing (Maver et al, 2015)

- Plant-based systems continue to play role in healthcare of 80% of world's developing countries
- Called "phytomedicines"
- Affordable and usually no to minimal side effects
- Level of evidence varies greatly

# Top 10 Selling Herbals in USA (2012)

- Cranberry
- Garlic
- Saw Palmetto
- Soy
- Ginkgo Biloba
- Milk Thistle
- Black Cohosh
- Echinachea
- St. John's Wort
- Ginseng

## Mainstream Markets

- Flax seeds
- Wheat and Barley grass
- Turmeric
- Aloe Vera
- Blue Green Algae
- Milk Thistle
- Elderberry
- Saw Palmetto
- Echinachea
- Cranberry

## Natural/Health Markets

# Practice Implications: Wound Care

- Need to identify detailed information on herbals used (dose, form, topical etc.)
- Need to identify “red-flag” medications for potential interactions (warfarin, digoxin, lithium, cyclosporine, protease inhibitors)
- Educate patient with wounds on safety, dosing, and potential toxicities of non-prescription pharmaceuticals (Ranade and Collins, 2014)

# Practice Implications: Wound Care

- Reduce polypharmacy for wound patients by "de-prescribing"; interact with primary care provider
- Remember that polypharmacy is not only removing excess drugs but that polypharmacy is also *going to more than one pharmacy* (Gillette et al, 2015); educate patients about the risk
- Put on your ARMOR and *LOOK* at the wound patient

# Practice Implications: ARMOR

- A: Assess
- R: Review
- M: Minimize
- O: Optimize
- R: Reassess

- **A**: Beers criteria; Beta blockers, Pain meds; Antipsychotics
- **R**: D-drug interaction; D-disease interaction; ADEs
- **M**: #of meds related to functional status
- **O**: for renal/hepatic status
- **R**: functional/cognitive status in one week from any changes and periodically

| Mnemonic | Meaning (Haque, 2008) |
| --- | --- |

# Practice Implications: Wound Care

- Update oneself about alternative adjuncts to wound healing
- Repurposed approved drugs: Erythropoietin (EPO); excellent review of animal studies using exogenous EPO (Hamed et al, 2014); topical EPO accelerates wound healing
- Phyto-extracts in wound healing-excellent overview (Ghosh and Gaba, 2013) 450 plant species have wound healing properties
- Hydralazine has anti-angiogenesis effects (study done in rats and chicken models) (Zheng et al, 2016)

# Summary

- Discussed multiple chronic conditions affecting wound patients
- Explored selected data for drugs that impair wound healing
- Offered implications for informed clinical practice

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