Better Living through Chemistry! -Dermatologic Therapies

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Disclosures

Advisory Board

- Bristol Myers Squibb -Psoriasis
- Incite -Vitiligo
- JDNPPA –Dermatology
- Leo –Atopic Dermatitis
- UCB -Psoriasis

Information presented is current as of 12/1/2024

Speaker Panel

- American Association of Nurse Practitioners -Dermatology
- Dermatology Nurses' Association -Dermatology
- MauiDerm NP+PA -Dermatology
- Nurse Practitioner Association for Continuing Education -Dermatology

Photo Courtesy V.Lazareth NP

Objectives

Upon completion of this activity, the participant will

- Describe the indications, considerations and potential adverse effects of topical agents used to treat dermatological diseases
- Discuss the indications, considerations and potential adverse effects of systemic agents used to treat dermatological diseases
- Identify the etiology, the various presentations and the commonly offending drugs associated with allergic drug reactions

Photo Courtesy V.Lazareth NP

I. Topical Pharmacology for Common Dermatology Disorders

Photo Courtesy V.Lazareth NP

Papulosquamous

Atopic Dermatitis, Psoriasis, Seborrheic Dermatitis

Photo Courtesy V.Lazareth NP

Question 1

Which is *NOT* a feature of Topical Corticosteroid Withdrawal?

A. more itch than burning

B. hx of prolonged, continuous use of mid- or high-potency TCS

C. confluent rather than patchy erythema

D. resembles atopic dermatitis but involves unusual sites

Photo Courtesy V.Lazareth NP

Topical Corticosteroids: vehicles

- active drugs are combined with a vehicle or base
- rate of penetration and of absorption depends on how *occlusive* the vehicle is
- solutions, lotions, gels, aerosols, foams
  - limited occlusion
  - useful on large surfaces and hair-bearing areas
- creams
  - less potent (less occlusive) than ointments
  - more tolerable than ointments, but may be drying
- ointments
  - more potent (more occlusive) than creams
  - more lubricating, less irritating than creams

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Topical Corticosteroids: classes

Potency Classes (examples)

- I Super-potent: clobetasol propionate, halobetasol propionate
- II Very High: fluocinonide, desoximetasone
- III High: fluticasone 0.05%
- IV Medium High: triamcinolone acetonide, hydrocortisone valerate ointments
- V Medium: triamcinolone acetonide cream, hydrocortisone valerate creams
- VI Low: desonide cream
- VII Very Low: hydrocortisone ointment or cream

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TCS: indications

Indications Papulosquamous Disorders

- Atopic Dermatitis
- Contact Dermatitis
- Discoid Lupus
- Lichen Planus
- Lichen Sclerosis
- Lichen Simplex Chronicus
- Nummular Dermatitis
- Psoriasis, etc.

Face & Intertriginous area

- Class VII cream or ointment (low potency)
- Class V agent if severe, then Class VI or VII for maintenance

Body

- Class III cream or ointment (medium to high potency)
- Class I-II agent if severe (x2 weeks max), then Class III-IV

*avoid fluorinated steroids in children, elders, on the face and in intertriginous areas

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TCS: potential adverse effects

- Skin Atrophy. shiny, thinning skin with telangiectasias; generally reversable
- Striae. linear atrophic scars are permanent; more likely to occur in intertriginous areas
- Acniform eruptions. erythema, papules, pustules, telangiectasias on the face (steroid rosacea, perioral dermatitis)
- Tinea Incognito. If misdiagnosed and treated with TCS, inflammation & itch may be reduced, but the superficial fungal infection will flare
- Hypersensitivity Reactions. Allergic Contact Dermatitis from the steroid, vehicle or both
- Purpura. from prolonged use of TCS; especially in elders
- Other local effects. hypopigmentation, excess facial hair growth, delayed wound healing
- Systemic effects. Hypothalamic-pituitary-adrenal axis suppression from excessive use of high potency TCS; especially in infants
- Tachyphylaxis: loss of efficacy when agent is used continuously for prolonged periods

Photo Courtesy V.Lazareth NP

AD –ACS Withdrawal

- adverse reaction presenting *after stopping* prolonged, inappropriate, or frequent use of topical corticosteroids
- erythema, edema, papular eruption, burning, stinging, itch, desquamation
- rash appears within days to weeks of discontinuing TCS
- rash develops only where the TCS was applied (though it may spread)
- flare may be worse than original rash

Consider TCS Withdrawal if

* more *burning* rather than itch
* *confluent* rather than patchy erythema
* resembles atopic dermatitis but involves unusual sites
* hx of prolonged continuous use of mid- or high-potency TCS

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TCS: withdrawal

TCS Withdrawal

- adverse reaction presenting *after stopping* prolonged, inappropriate, or frequent use/abuse of topical corticosteroids

Treatment

- tapering vs abrupt discontinuation of TCS has not been determined
- consider a tapering course of *oral* steroids
- oral tetracycline or low-dose isotretinoin (steroid rosacea, perioral dermatitis)

Prevention: Pulse Dosing

- TCS: 2 days on - 5 days off *(or)* 2 weeks on - 2 weeks off
- alternate TCS with ceramide moisturizers –AD
- alternate TCS with topical Vit D analog (calcipotriene) –PS
- alternate TCS with TCI (tacrolimus, pimecrolimus) –AD or PS

Photo Courtesy V.Lazareth NP

TCS: combination product

halobetasol 0.01% - tazarotene 0.045%

- topical corticosteroid + topical retinol lotion daily
- I: **psoriasis**
- CI: pregnancy, caution with lactation
- negative HCG prior to start, effective birth control during treatment
- AE: redness, itching, swelling, burning, stinging, application site pain, folliculitis, skin atrophy, peeling, rash. Cushing's, hyperglycemia, cataracts, glaucoma
- Efficacy: 36% at least a 2-grade improvement from baseline in Investigator's Global Assessment (IGA) score + clear/ almost clear at week 8

Photo Courtesy V.Lazareth NP

Topical Calcineurin Inhibitors

tacrolimus 0.1% / 0.03% ointment	pimecrolimus 1% cream
• ≥2 yr; applied daily • steroid sparing agent which reduces symptoms of **atopic dermatitis** • helpful to avoid steroidal effects at the face, intertriginous sites • AEs: burning, itching, sensitivity, folliculitis flu-like symptoms	• ≥2 yr; applied BID • steroid sparing agent which reduces symptoms of **atopic dermatitis** • AE: less irritating & greasy than tacrolimus

In 2005, the Pediatric Advisory Committee of the US FDA implemented a 'black box' warning for tacrolimus ointment and pimecrolimus cream due to the lack of long-term safety data and the potential risk of the development of malignancies. This warning was extrapolated from systemic tacrolimus (lymphoma, SCC) but has not been borne out with topical immunomodulators

Photo Courtesy V.Lazareth NP

Topical phosphodiesterase-4 Inhibitors

crisaborole ointment

- apply BID
- I: topical treatment of mild - moderate **atopic dermatitis**
- pts ≥2 yrs of age
- CI: pregnancy, lactation
- AE: burning, stinging

roflumilast 0.3% cream

- apply daily
- I: **atopic dermatitis, plaque psoriasis**
- pts ≥6 yrs of age
- CI: pts with moderate to severe liver impairment (Child-Pugh B or C)
- AE: diarrhea, headache, insomnia, nausea, application site pain, URI, UTI
- Efficacy: DERMIS-1 and DERMIS-2 showed ~40% 2-grade improvement from baseline: clear/ almost clear wk 8

https://www.arcutis.com/wp-content/uploads/USPI-roflumilast-cream.pdf

Photo Courtesy V.Lazareth NP

Topical phosphodiesterase-4 Inhibitors

roflumilast 0.3% foam

- apply daily
- I: **seborrheic dermatitis**
- pts ≥9 yrs of age
- boosts cAMP to create an anti-inflammatory effect
- can be used on all affected areas of the body, including hair-bearing areas
- no limit to how long it can be used

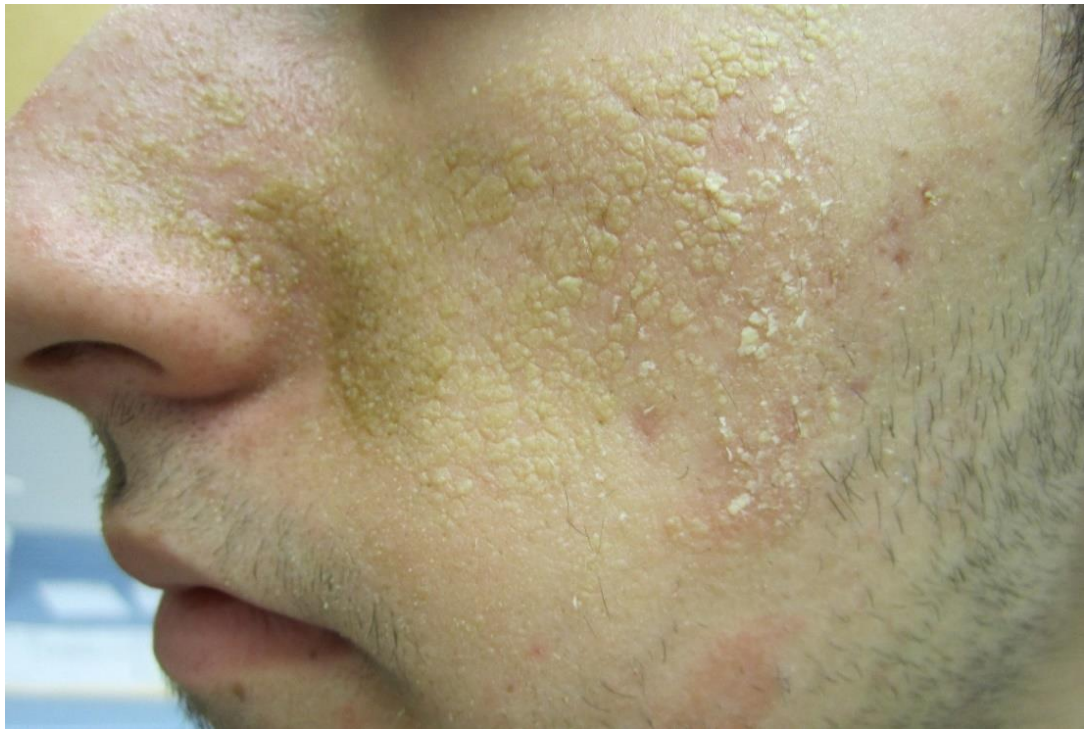


Photo Courtesy V.Lazareth NP

Topical JAK Inhibitor

ruxolitinib 1.5% cream

- apply BID up to 20% BSA
- JAK1 + JAK2 inhibitor
- I: mild to moderate **atopic dermatitis**
- topical short-term and non-continuous chronic treatment in immunocompetent pts ≥12 yr whose disease is not adequately controlled with topical Rx therapies (TCS, TCI)
- AEs: nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, rhinorrhea
- Efficacy: TRuE-AD1 & 2: 52% clear/near clear & itch reduction

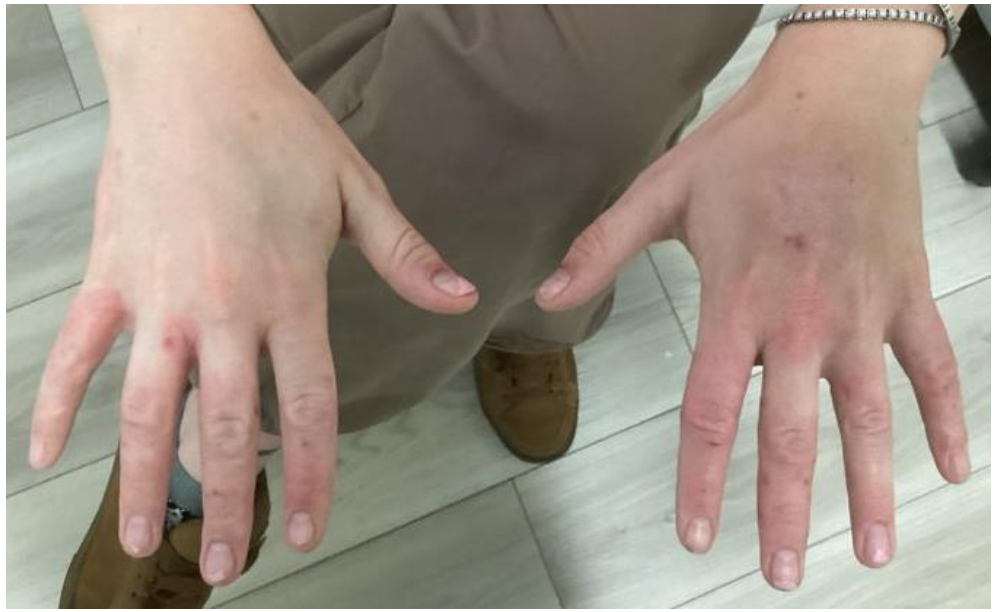


Photo Courtesy V.Lazareth NP

Topical non-steroidal aryl hydrocarbon

tapinarof 1% cream

- apply daily
- I: once-daily non-steroidal topical treatment of plaque **psoriasis** in adults
- non-steroidal aryl hydrocarbon Th17 & Th2 receptor agonist reduces inflammation
- downregulation of pro-inflammatory cytokines (IL-17) and normalization of skin barrier proteins (filaggrin) with an anti-inflammatory effect
- CI: pregnancy, lactation
- AEs: folliculitis, nasopharyngitis, contact dermatitis, headache, pruritus, flu
- PSOARING 1 & 2: 36%/40% clear/nearly clear

C Kontzias, SR Feldman. *More New Therapeutics for Psoriasis. Cutis*. 2023 February;111(2):63-64 | doi:10.12788/cutis.0699

Photo Courtesy V.Lazareth NP

Adnexal

Acne, Rosacea, Hyperhidrosis, Alopecia, Onychomycosis

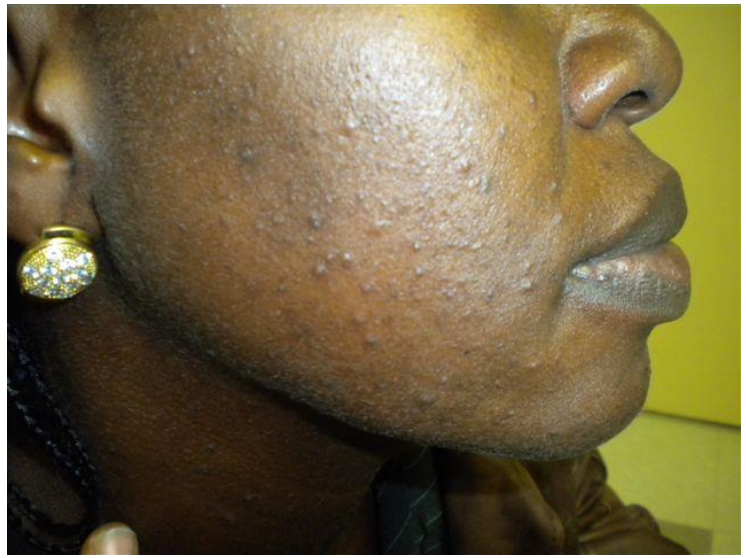
Photo Courtesy V.Lazareth NP

Question 2

You are seeing 14-year-old Tamara for follow-up of her persistent moderate comedoneal acne. Today her 8-year-old sister Jasmine is scheduled for evaluation of her acne as well. Their mother has been reminding both girls to apply adapalene (Differin®) lotion at bedtime, but the blackheads are getting worse. She requests a prescription of trifarotene (Aklief®) cream for both girls as it has worked well for her niece.

You prescribe trifarotene (Aklief®) 0.005% cream for

A. both Tamara and Jasmine
B. only Tamara
C. only Jasmine
D. neither Tamara or Jasmine



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Topical Retinoids

I: **acne, hyperpigmentation**

Low strength
- adapalene 0.1% lotion
- tretinoin 0.025% cream
- tazarotene 0.05% cream

High strength
- adapalene 0.3% gel
- tretinoin 0.05% or 1% gel
- tazarotene 0.1% gel
- tazarotene aqueous foam

trifarotene 0.005% cream daily
- selective retinoic acid receptor gamma agonist
- increased efficacy, decreased irritation
- for facial & truncal acne
- pts > 9 yrs old

tretinoin 0.05% lotion daily
- hydrating ingredients (soluble fish-derived collagen, glycerin, sodium hyaluronate) which minimize irritation
- marketed to women with acne
- pts > 9 yrs

Photo Courtesy V.Lazareth NP

Topical Retinoids: Pt Education

Retinoids
- are the mainstay of acne therapy
- clear both open and closed comedones
- minimize hyperpigmentation and scarring

Side Effects
- erythema, dryness, scaling, flaking, stinging, burning

Caution
- Inform your provider if you have eczema or a fish allergy
- Discontinue all retinoids in pregnancy, lactation

Counseling
- apply sparingly at hs >1 hr after washing
- use a very gentle cleanser
- apply non-comedogenic moisturizer daily
- avoid ultraviolet light, sunlamps, tanning, scrubs, extreme cold, wind

Photo Courtesy V.Lazareth NP

Topical Antibiotics

- minocycline foam 4%
  inflammatory lesions of moderate to severe **acne vulgaris** in patients aged ≥ 9 yrs
  developed to minimize systemic minocycline absorption and toxicity
  AEs uncommon (no phototoxicity, photoallergy, skin sensitization or irritation)
  caution: TCN allergy. discontinue in pregnancy, lactation

clindamycin 1% gel, lotion, solution, pledget, foam

- applied across acne areas once or twice daily in pts >12 yrs old
- use in conjunction with benzoyl peroxide to minimize resistance
- contraindications: hypersensitivity; colitis, enteritis

erythromycin 2% gel

- applied across acne areas once or twice daily
- high level of resistance; use in conjunction with benzoyl peroxide
- may temporarily stain skin, clothing, linens

Photo Courtesy V.Lazareth NP

Topical combination product

clindamycin phosphate, adapalene and benzoyl peroxide Topical Gel 1.2%/0.15%/3.1%

- applied once daily to treat acne vulgaris in pts ≥12 years
- AE: application site reactions, pain, erythema, dryness, irritation, exfoliation, dermatitis.
- nearly 50% Clear or Almost Clear and 2-Grade Reduction from Baseline

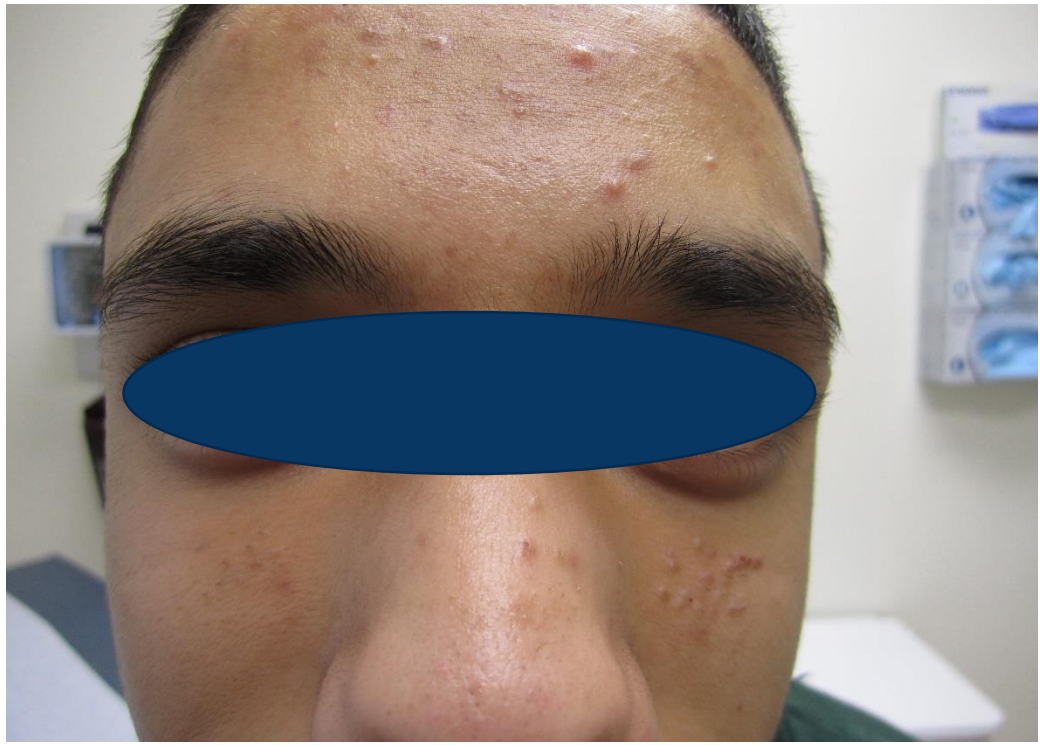
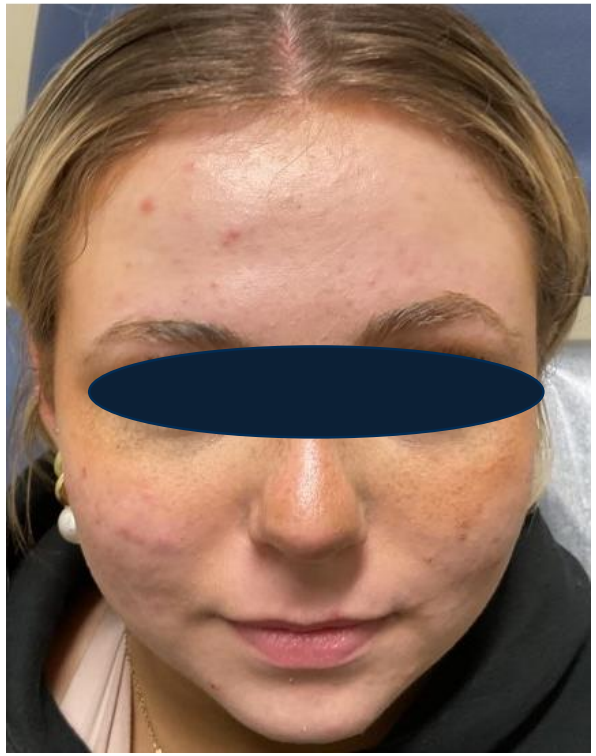


Photo Courtesy V.Lazareth NP

Topical androgen receptor inhibitor

clascoterone 1% cream

- androgen receptor inhibitor to reduce cutaneous hormones (sebum, inflammation)
- apply BID to treat acne vulgaris >12 yr
- AEs: adrenal insufficiency, hyperkalemia
- skin irritation including itching, burning, skin redness, peeling
- Caution: eczema. discontinue in pregnancy, lactation
- Counseling: use a very gentle cleanser and non-comedogenic moisturizer



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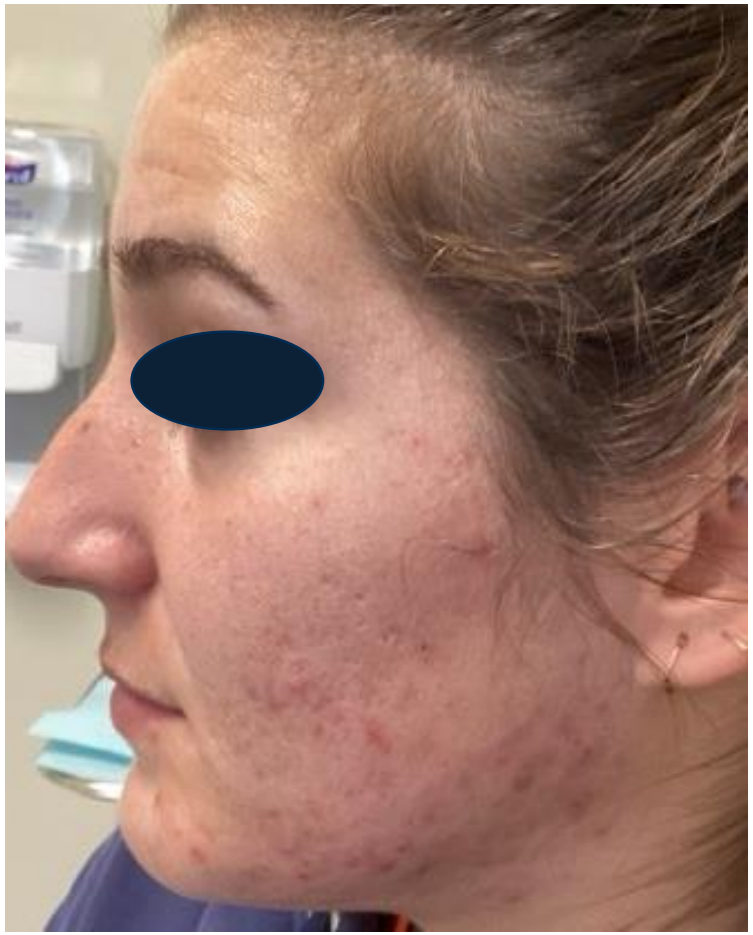
Topical Hormone

dapsone 7.5% gel

- daily in pts > 9 yrs
  adult female inflammatory acne
- avoid in pts taking oral dapsone, antimalarials, TMP/SMX or with congenital or idiopathic methemoglobinemia
- methemoglobinemia from topical dapsone is relatively uncommon due to relatively poor absorption through the skin and appears only in case reports
- AEs: dryness, pruritus. dapsone gel with benzoyl peroxide may result in temporary local yellow discoloration of skin and facial hair



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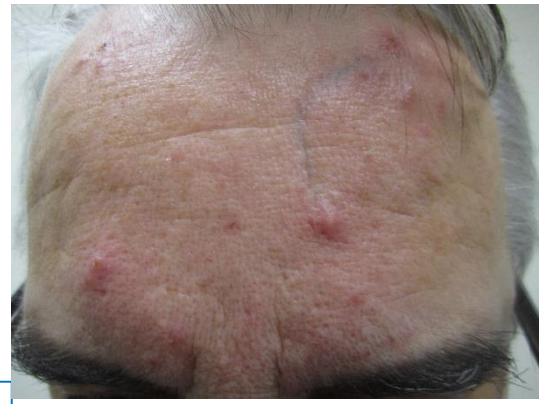
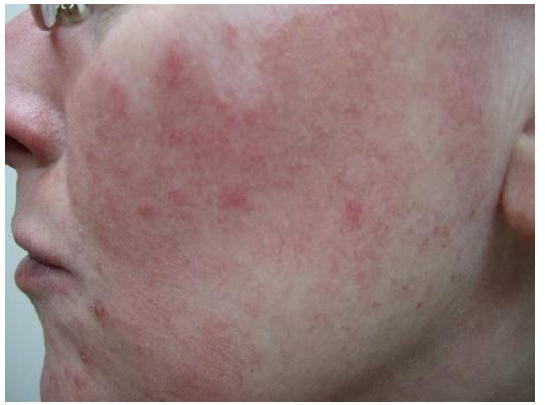
Topical anti-inflammatory



- Rosacea: papules and pustules
- metronidazole 1% cream or (Metrogel®) 1% gel daily, metronidazole 0.75% cream BID. AE: minimal irritation
- azelaic acid 15% cream or (Finacea®) 15% gel or foam BID AE: may lighten skin, gel may be irritating
- ivermectin 1% cream daily
  AEs: burning, irritation, pruritus, dry skin; usually transient
- sodium sulfacetamide 10% & sulfur 5% cream, lotion, wash
  Note: tinted preparations reduce the erythema of rosacea

Photo Courtesy V.Lazareth NP

Topical alpha 1A adrenoceptor agonists



brimonidine 0.33% gel

- daily
- I: rosacea: erythema
- alpha adrenergic agonist
  AEs: flushing, erythema, nasopharyngitis, burning, headache increased IOP.
- Post-marketing: bradycardia, hypotension, angioedema, pallor, hypersensitivity, urticaria, dizziness

oxymetazoline 1% cream

- I: rosacea: erythema
- alpha 1A adrenoceptor agonist
- warnings: CV disease, orthostatic hypotension, cerebral /coronary insufficiency, Raynaud's, thromboangiitis obliterans, scleroderma, Sjögren's syndrome, narrow-angle glaucoma
- AEs: dermatitis, erythema, pain, inflammatory rosacea lesions

Photo Courtesy V.Lazareth NP

Topical anticholinergic

sofpironium 12.45% gel

- July 2024. for the treatment of underarm hyperhidrosis for pts ≥9 yrs
- anticholinergic/antimuscarinic medication that blocks sweating at the level of the sweat glands
- 85% of patients experienced a clinically meaningful improvement in their condition.
- >60% of study participants had ≥50% reduction in sweat production
- AEs: dry mouth, blurred vision

SweatControl Patch

- April 2023. SweatControl Patch™ for excessive underarm sweating (adults)
- applied by provider for ~3 minutes
- targeted alkali thermolysis: interaction between sweat and the patch generates a targeted amount of heat, causing microthermal injury to the sweat glands
- 60% had >50% decreased sweat production x 2-4 mo
- 20% slight redness or slight swelling that resolved within 2 weeks

Photo Courtesy V.Lazareth NP

Topical anticholinergic

glycopyrronium 2.4% cloth

- applied daily
- topical anticholinergic
- I: axillary hyperhidrosis in pts ≥9 yrs
- most experience noticeable decrease in sweating severity after 1 week
- studies report a reduction of sweat volume by ≥50%
- well-tolerated, non-invasive treatment option

onabotulinumtoxin A ID injection

- 2004. onabotulinumtoxin A approved for the treatment of primary axillary hyperhidrosis in adults
- A provider injects Botox by ID injection
- In one clinical study >80% of pts achieved >50% reduction in sweating
- 50% achieved relief for at least 201 days, some, for >1 year

Photo Courtesy V.Lazareth NP

Non-Scarring Alopecia

minoxidil 2% or 5% foam

- applied to scalp BID
- I: non-scarring alopecia (androgenetic hair loss)
- Response takes several months
- Response lasts only as long as the medicine continues to be used
- Pregnancy: “C”. Lactation: appears safe
- safety not established in pediatrics

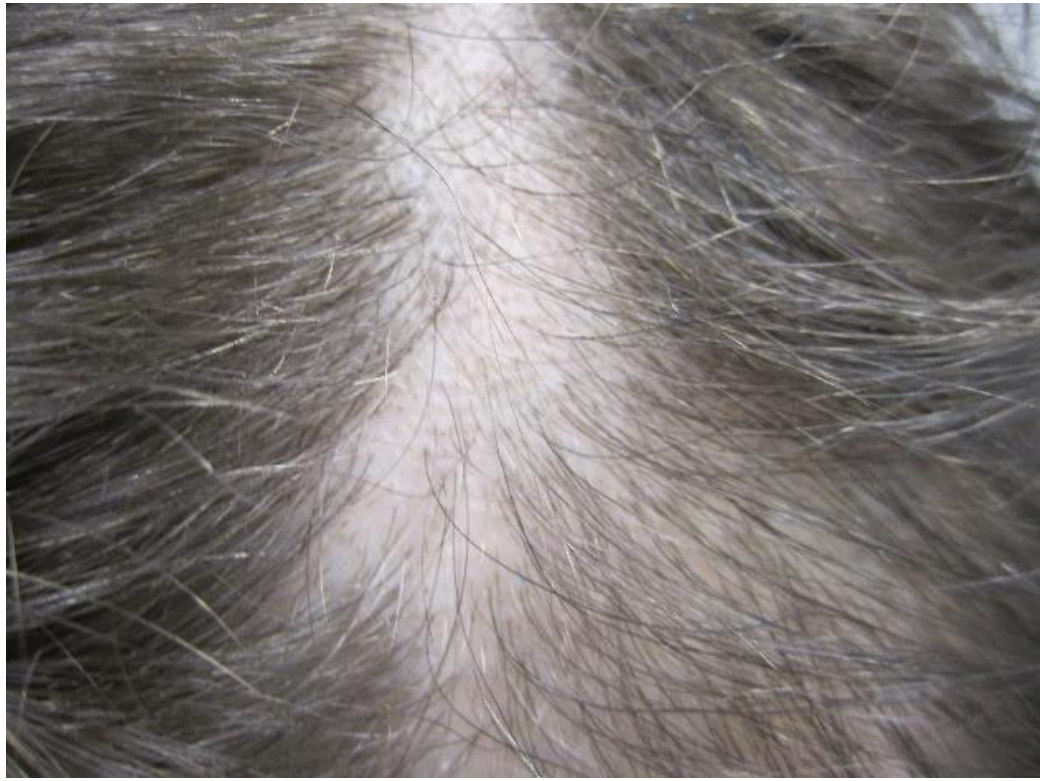


Photo Courtesy V.Lazareth NP

Onychomycosis

efinaconazole 10% topical solution
tavaborole 5% solution

- topical treatment of onychomycosis (tinea unguium) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*
- applied to affected toenails daily for 48 wks
- Pregnancy: (C). safety in pediatrics not established
- AEs: ingrown toenail, application-site dermatitis, application-site vesicles, and application-site pain
- efficacy: complete cure ~16%, mycologic cure ~55%

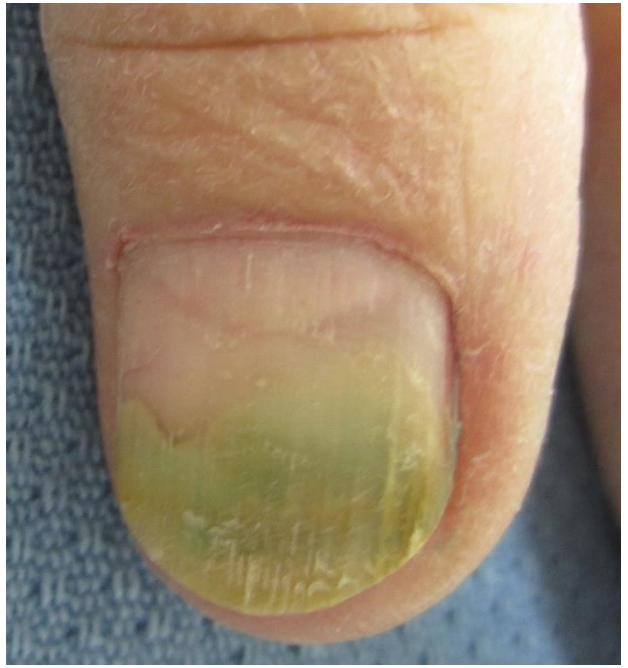


Photo Courtesy V.Lazareth NP

Pre-Cancerous & Malignancy

Photo Courtesy V.Lazareth NP

Actinic Keratoses: field therapy

tirbanibulin ointment daily x 5 days to AKs face or scalp x 25 cm2

- AEs: itching, pain, redness, flaking, scaling, crusting, swelling, blisters, peeling, ulcers
- pooled analysis of 702 pts from 2 Phase 3 studies : 49% Klisyri® pts vs 9% vehicle

Photodynamic therapy (PDT)

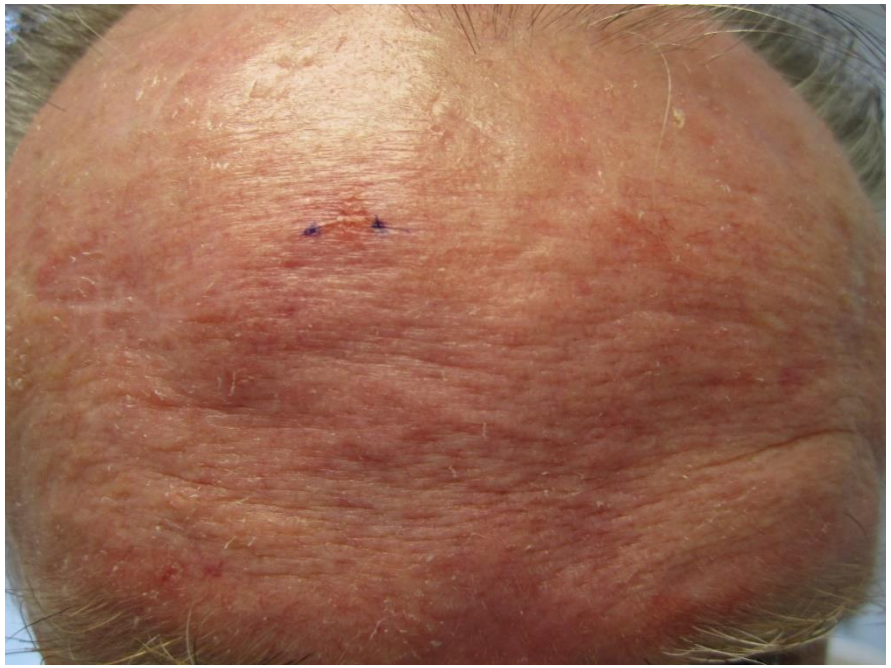
- topical 5-aminolevulinic acid + blu light
- uses specific wavelengths of light to photo-excite solution of porphyrins that have been applied to damaged skin
- increased energy is rapidly absorbed by adjacent tissue oxygen, causing formation of singlet oxygen radicals which react to destroy adjacent tissue
- FDA-approved for AK, sBCC, small, low risk nBCC: cure rates 70 - 90%

Photo Courtesy V.Lazareth NP

Actinic Keratoses : field therapy

topical 5-fluorouracil cream, solution

- stop treatment when erosions, ulceration, or necrosis develop
- AK cure rates 80 – 90%
- AEs: photosensitivity, inflammation, crusting, erosions



**FDA approved for superficial BCC and small, thin BCCs on trunk and extremities: fluorouracil 5% cream BID x 6 – 12 wks

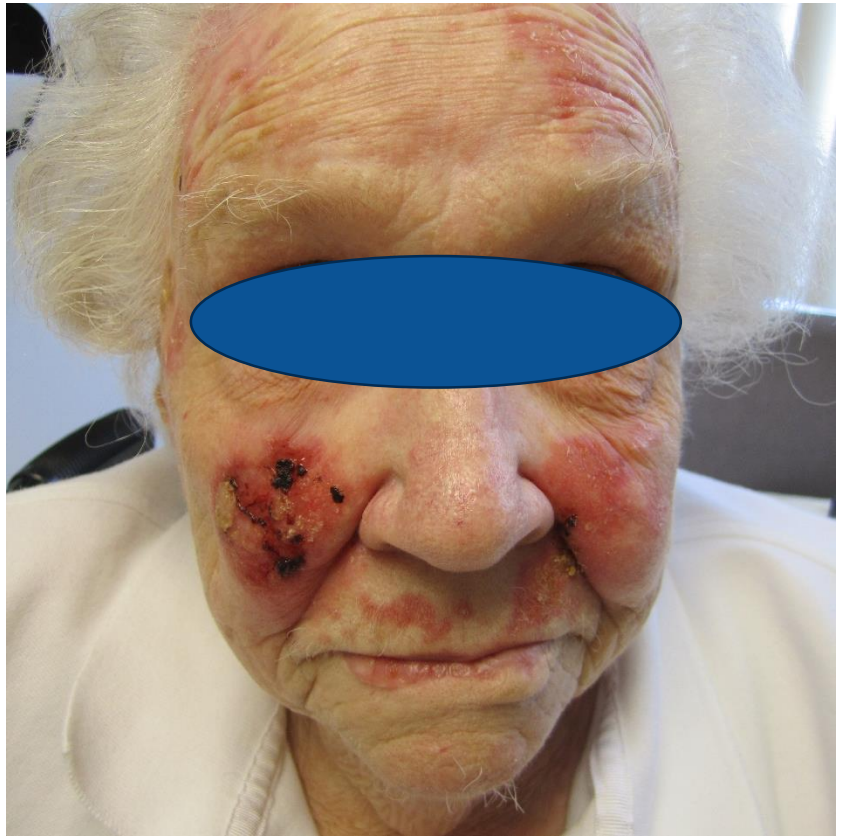
Photo Courtesy V.Lazareth NP

Actinic Keratoses : field therapy

imiquimod cream

- avoid nostrils, eyes; caution with autoimmune condition
- AEs: flu-like symptoms, hypopigmentation

**FDA approved for SCC in situ:
imiquimod 5% cream 5 d/wk for 6 – 12 wks



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Cutaneous T-cell Lymphoma

nitrogen mustard 0.016% gel

- apply daily
- alkylating topical chemotherapy
- I: topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in pts who have received prior skin-directed therapy (bexarotene)
- CI: mucous membranes
- AE: dermatitis, pruritus
  bacterial skin infection, skin ulceration, blistering hyperpigmentation, non-melanoma skin cancers

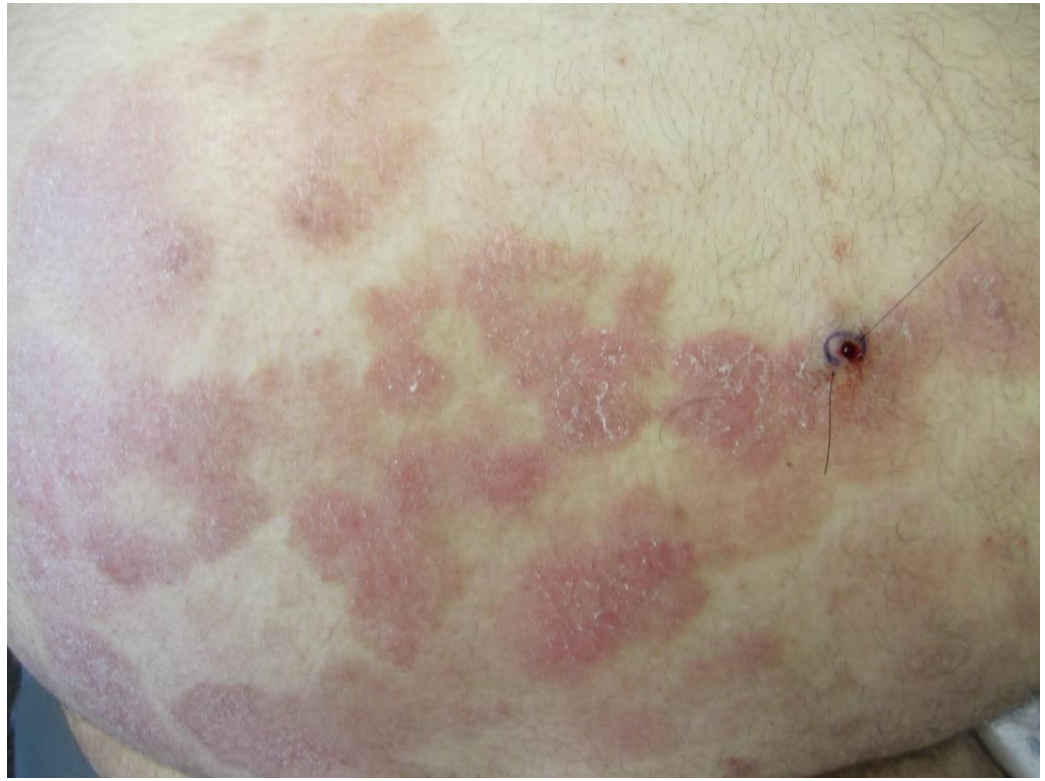


Photo Courtesy V.Lazareth NP

Drug Safety in Pregnancy

- half of all pregnancies are unplanned and on average, pts realize they are pregnant at 5.5 wks risking unintended fetal exposure
- 2014 “Pregnancy and Lactation Label Ruling” (PLLR)
  - drug is not absorbed
  - presence of drug in human milk
  - effect of drug on breastfed child / effect of drug on milk production
- topical corticosteroids
  - potent or very potent TCS may be associated with an increased risk of low birth weight
- topical antiparasitics
  - permetherin is safe, avoid lindane
- topical antifungals
  - nystatin, clotrimazole, miconazole, ketoconazole: safe
  - avoid terbinafine, naftifine, ciclopirox

Truong, Thu Minh PharmD1; Yaghi, Marita MD2; Murase, Jenny MD3,4. Dermatologic Drug Safety in Pregnancy. Journal of Dermatology for Physician Assistants 17(3):p 1-12, Summer 2023. | DOI: 10.58744/001c.88954

Photo Courtesy V.Lazareth NP

Drug Safety in Pregnancy

- topical hydroquinone, glycolic acid, salicylic acid, benzoyl peroxide: no safety signals
- topical minoxidil: avoid in pregnancy
- topical antivirals
  - Acyclovir (famciclovir, valacyclovir): safe
  - HPV: LN2, tricholoracetic acid: safe
  - Peri-ungual warts: squaric acid, IL candida. Avoid cantheradin, imiquimod, podofilox
- topical PDE4 inhibitors
  - crisaborole: ≥3 mo (AD), minimal absorption
  - roflumilast: ≥6 yr (AD, PS), no recommendation during pregnancy but avoid in labor and delivery
- topical non-steroidal aryl hydrocarbon
  - tapinarof (PS): no recommendation during pregnancy or lactation

Truong, Thu Minh PharmD1; Yaghi, Marita MD2; Murase, Jenny MD3,4. Dermatologic Drug Safety in Pregnancy. Journal of Dermatology for Physician Assistants 17(3):p 1-12, Summer 2023. | DOI: 10.58744/001c.88954

Photo Courtesy V.Lazareth NP

Drug Safety in Pregnancy

- topical calcineurin inhibitors
  - tacrolimus, pimecrolimus: ≥2 yr (AD), avoid in pregnancy
- topical vitamin D3 derivative
  - calcipotriene: should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, caution in lactation
- topical JAK inhibitors
  - avoid during pregnancy and lactation due to limited safety data
- Phototherapy
  - (UVB) safe with folic acid supplementation, avoid psoralen
- Procedures
  - lidocaine, lidocaine with epinephrine: safe

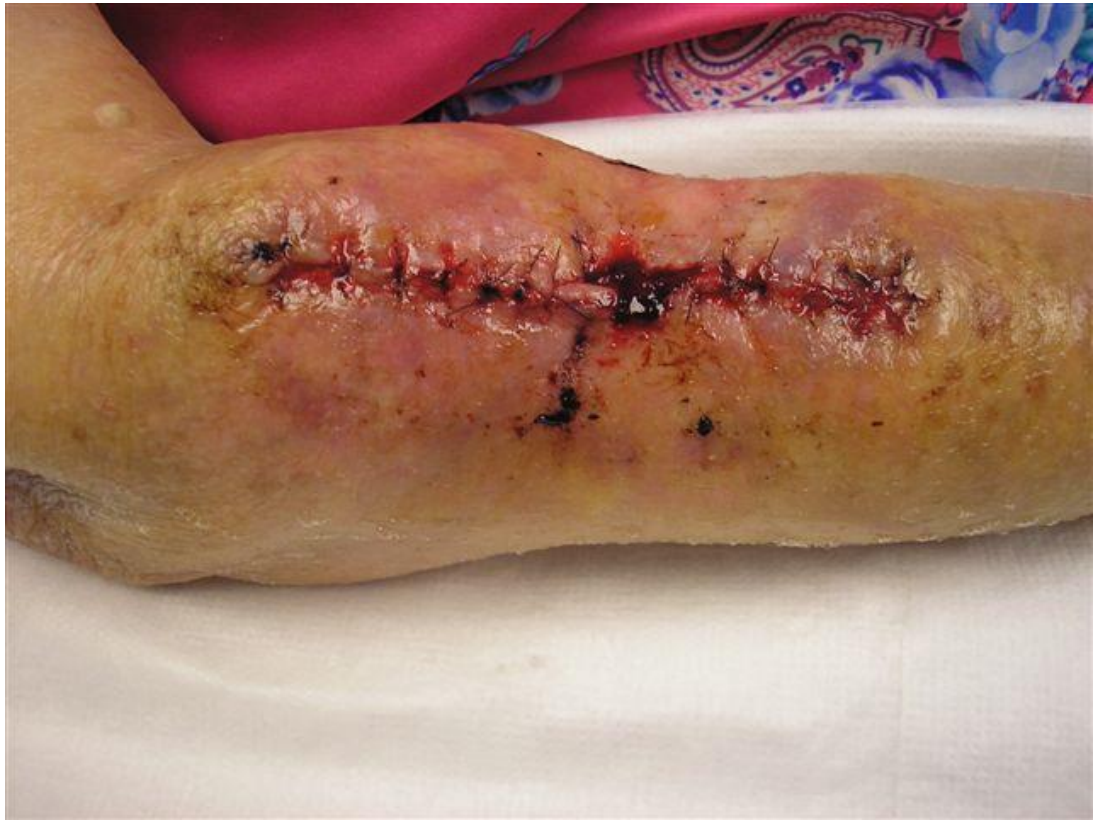
Truong, Thu Minh PharmD1; Yaghi, Marita MD2; Murase, Jenny MD3,4. Dermatologic Drug Safety in Pregnancy. Journal of Dermatology for Physician Assistants 17(3):p 1-12, Summer 2023. | DOI: 10.58744/001c.88954

Photo Courtesy V.Lazareth NP

II. Systemic Pharmacology for Dermatological Diseases

Photo Courtesy V.Lazareth NP

I. Anti-Infectious



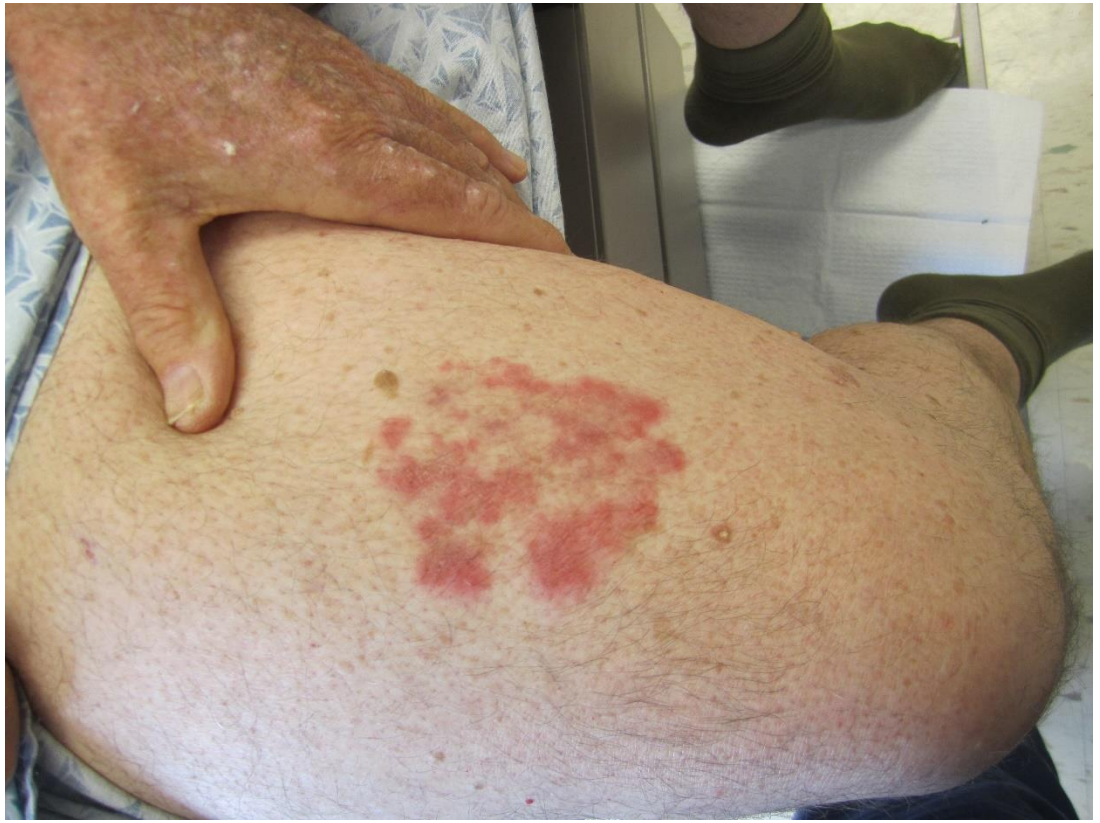


Photo Courtesy V.Lazareth NP

Question 1

- The Lyme titres for your 36 yr female pt who had a tick attached to her thigh for 2 days have returned as positive. You prescribe a 21 day course of doxycycline 100 mg BID. You explain to the pt that while doxycycline is not always easy to tolerate, it is extremely important to complete the entire course.
- You explain all of the following *except*:
- A. avoid sun exposure
- B. avoid taking with antacids
- C. minimize fluid intake
- D. vaginal yeast infections and diarrhea are common

Photo Courtesy V.Lazareth NP

Systemic Tetracyclines:

doxycycline, minocycline

FDA approved: acne, rickettsial (Rocky Mtn Spotted Fever), spirochetal (Lyme), genital (gonorrhea, chlamydia), zoonoses (plague, tularemia), anthrax, aquatic injuries

AE: GI distress, photo toxicity, vestibular toxicity, blue-black pigmentation. (rare) drug hypersensitivity, SJS, pneumonitis, drug-induced lupus, serum sickness (MCN)

Pt Education

- avoid excessive sunlight or artificial ultraviolet light
- drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration
- absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk
- absorption of tetracyclines is reduced when taken with antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron containing preparations
- doxycycline might increase the incidence of vaginal candidiasis
- diarrhea is common

Photo Courtesy V.Lazareth NP

Question 2

A seasoned PA has been treating pts with mild to significant fungal infections for years. The mycoses usually resolve with topical therapy, but she has occasionally prescribed systemic antifungals. She recently read an article which alerted her to new Black Box Warnings which include all of the following *EXCEPT*:

A. Itraconazole is contraindicated in pts with CHF

B. Itraconazole is contraindicated in pts with COPD

C. ketoconazole can cause hepatotoxicity resulting in liver transplantation or death

D. ketoconazole can cause adrenal insufficiency by decreasing production of corticosteroids

Systemic Antifungals:
terbinafine, itraconazole, griseofulvin, fluconazole, ketoconazole

FDA approval

- onychomycosis: terbinafine, itraconazole, griseofulvin
  cutaneous tinea: griseofulvin
  vaginal candidiasis: fluconazole, ketoconazole
  chronic mucocutaneous candidiasis: ketoconazole
  blastomycosis, histoplasmosis: itraconazole, ketoconazole
  aspergillosis: itraconazole
  cryptococcal meningitis: fluconazole
  chromoblastomycosis, coccidomycosis, paracoccidiomycosis: ketoconazole

Contraindications

- fluconazole: liver disease, dysrhythmias, cytochrome p-450 drugs
  griseofulvin: liver failure, porphyria, PCN allergy, OCP
  itraconazole: CHF, CRF, cytochrome p-450 drugs
  terbinafine: chronic liver or kidney disease, cytochrome p-450 drugs
  ketoconazole: cytochrome p-450 drugs

itraconazole is not contraindicated with COPD

Photo Courtesy V.Lazareth NP

Question 3

A 39 yr pt s/p renal transplant develops painful grouped vesicles and crusted erosions at the right forehead, right upper lid and nose which do not cross midline. He is started on treatment and develops abrupt onset of fever, petechiae, confusion and thrombocytopenia.

Which medication was he most likely being treated with?

A. acyclovir
B. foscarnet
C. prednisone
D. IVIG
E. valacyclovir

Photo Courtesy V.Lazareth NP

Systemic Antivirals:
valacyclovir, famcyclovir, acyclovir

FDA Approval

- herpes simplex (primary, recurrent, suppressive), varicella, zoster and subsets: gingivostomatitis, herpes labialis & gladiatorum, eczema herpeticum, herpetic whitlow & keratoconjunctivitis

Caution

- renal disease, immune suppression

high dose valacyclovir in transplant pts is associated with severe, sometimes fatal, cases of thrombocytopenic purpura/hemolytic uremic syndrome

AE

- GI distress, headache, mood/behavior effects, Acute renal failure, CNS effects Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (in advanced HIV, bone marrow and renal transplant pts)

Photo Courtesy V.Lazareth NP

II. Anti-proliferative

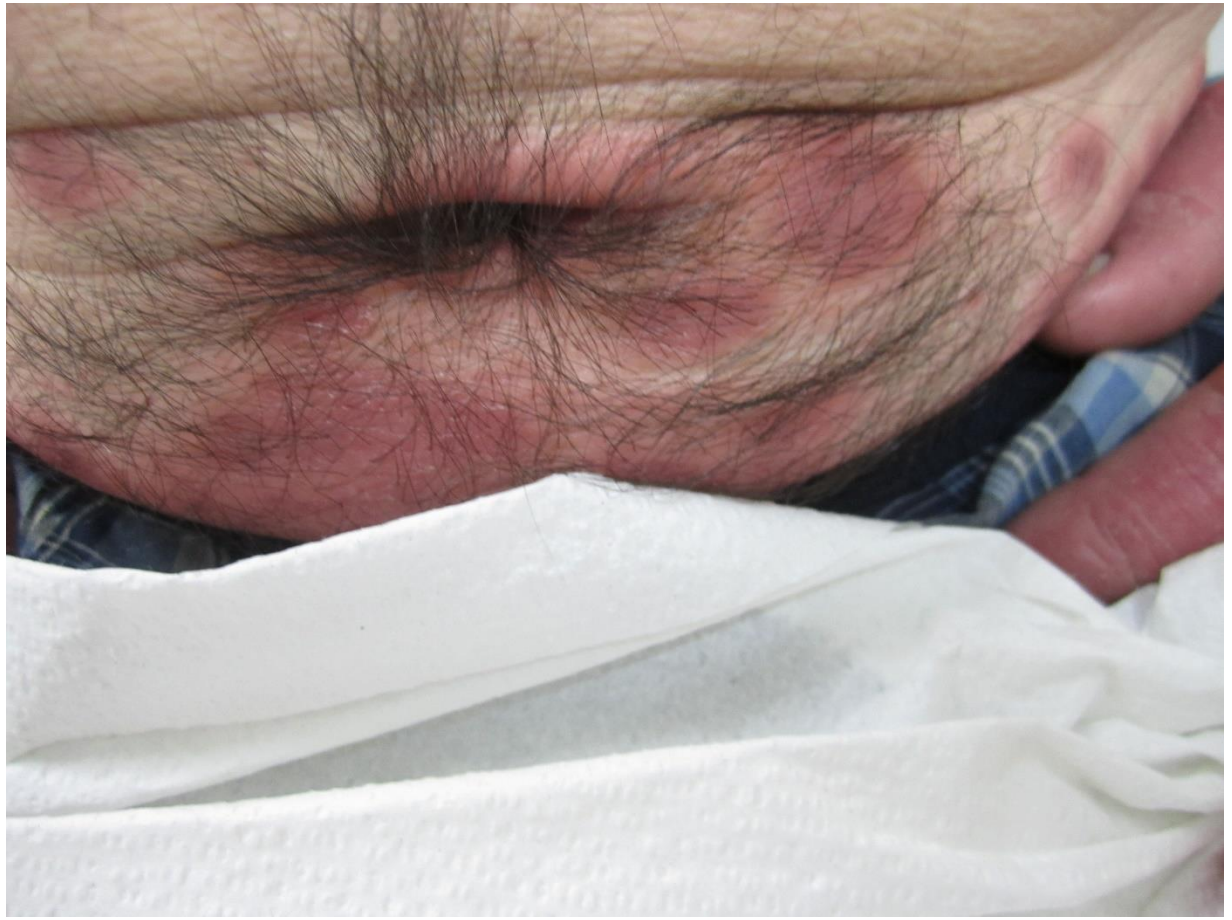


Photo Courtesy V.Lazareth NP

QUESTION 4

A 42 yr old male with a history of type II diabetes and hypertension is newly diagnosed with plaque psoriasis on 20% BSA. He does not drink alcohol or use NSAIDS. You discussed the comorbidities of psoriasis and the importance of routine health maintenance. Management options include methotrexate.

Which screening test are you *LEAST LIKELY* to order before initiating therapy?

A. tuberculosis screening
B. liver biopsy
C. endoscopy
D. renal function studies

methotrexate

FDA approved

- psoriasis, cutaneous T cell lymphoma
- folic acid 1 mg daily should be given concomitantly with MTX to reduce pancytopenia, GI side effects

Contraindications

- AIDS, blood - bone marrow disorders, immunodeficiency, liver disease, decreased renal function, pts contemplating pregnancy

Adverse Effects

- teratogenic, liver - renal toxicity, lymphoma, MTX-induced cirrhosis, rash, fatigue, confusion, fever, chills, shortness of breath, dry cough, palpitations, bleeding or bruising, urinary frequency

There is no indication for baseline endoscopy. MTX is an immunosuppressant (TB). Baseline liver biopsy should be considered for pts with risk factors for hepatoxicity (DM). MTX is excreted from the kidney (renal function).

Photo Courtesy V.Lazareth NP

methotrexate -monitoring

Monitoring

- CBC, serum creatinine, and transaminases weekly for the 1st 4 weeks and then at least bimonthly: (a sudden dip in blood counts must alert to bone marrow toxicity as myelosuppression can occur due to folate deficiency)
- Liver function tests (monitoring serum AST, ALT, and serum albumin levels)
- Creatinine clearance: (50 ml/min is necessary before prescribing methotrexate)
- Tuberculosis testing: (MTX can cause reactivation of tuberculosis)
- Baseline chest radiographs: to detect interstitial and alveolar infiltrates, hilar adenopathy, pleural effusions, and pulmonary fibrosis.

Methotrexate Pneumonitis

- dry cough, shortness of breath, fever. diffuse interstitial pattern on x-ray especially in elders. hx of lung disease, prior use of DMARDs, low albumin, diabetes

III. Miscellaneous: dapsone, antimalarials

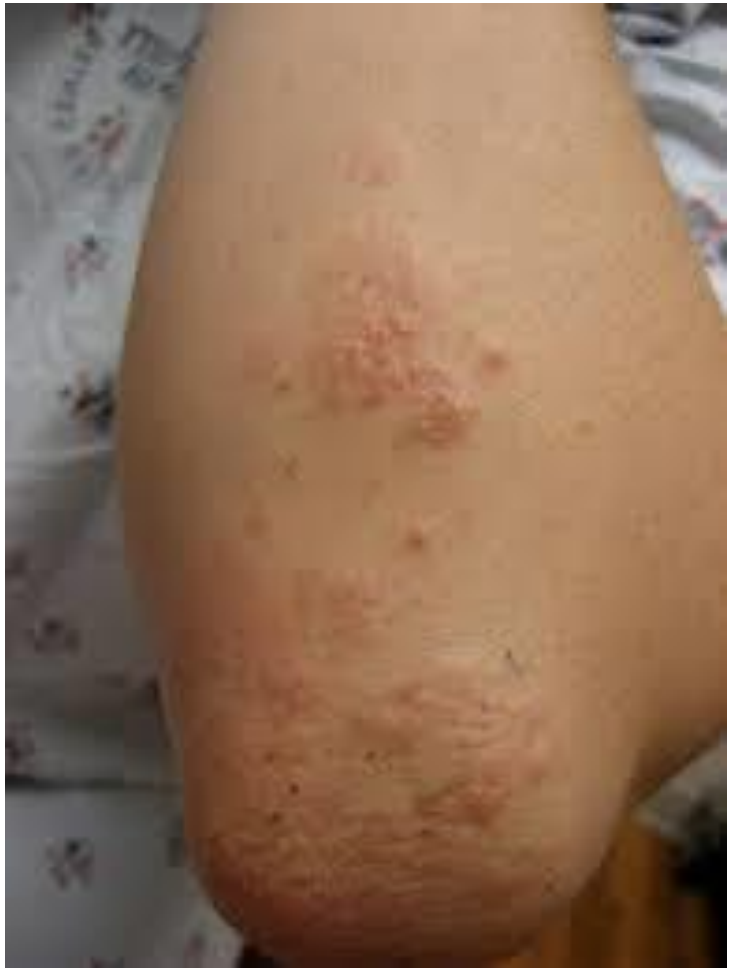


Photo Courtesy V.Lazareth NP

QUESTION 5

You started a 40 yr male on dapsone 50mg daily for his recently diagnosed dermatitis herpetiformis. Weekly lab results have been normal. He returns for follow up after 4 weeks of therapy and complaints of increasing shortness of breath and fatigue.

You discontinue the dapsone and order:

A. Chest xray

B. Reticulocyte count

C. IgE

D. Methemoglogin level

dapsone

FDA approved

- Dermatitis herpetiformis; leprosy

AE

Methemoglobinemia (high amount of methemoglobin is made in the blood preventing oxygen release into tissues -blue lips, HA, lethargy). Hemolytic anemia (weakness, SOB, severe fatigue). Hypersensitivity (fever, fatigue, rash, ST, lymphadenopathy). Agranulocytosis (persistent fever, usually within first 8 wks of treatment). Urticaria (hives lasting <24 hrs). Hepatitis (jaundice).

Monitoring

- CBC-diff, Renal function, Liver function, UA
- Reticulocyte count (hemolysis)
- baseline Methemoglobin and G6PD levels (deficiency can cause severe hemolysis especially in pts with African, Middle Eastern, Asian ancestry)

Hemolytic anemia usually occurs to some degree in all pts on dapsone therapy. Severe hemolysis usually occurs within the first 6-8 wks. A reticulocyte count is the most accurate measure.

Photo Courtesy V.Lazareth NP

QUESTION 6

A 47 yr female with a history of systemic lupus erythematosus has been referred by her PCP for pigmentary problems. She complains of a sudden onset of whitening at the roots of her hair. She has also developed a blue-gray discoloration at her forehead and nail beds. The ROS is otherwise unremarkable. Which medication do you suspect may be the cause?

A. hydroxychloroquine (Plaquenil®)

B. spironolactone

C. cyclophosphamide

D. mycophenolate mofetil

Photo Courtesy V.Lazareth NP

hydroxychloroquine

FDA Approval

- subacute/cutaneous lupus erythematosus (SCLE/SLE)
  Off label: polymorphous light eruption, sarcoidosis (PMLE), granuloma annulare, GVHD, panniculitis, lichen planus

AE

- blue-gray to black discoloration (shins, face, palate, nail beds), bleaching of hair roots, exanthem, N/V. (rare) retinopathy, vision changes, pancytopenia, hemolysis

Monitoring

- baseline: EKG, CBC, CMP, G6PD, liver enzymes

  baseline + q 6-12 mo. ophthalmology exam

Adverse effects of hydroxychloroquine include blue-gray to black discoloration (shins, face, palate, nail beds), bleaching of hair roots, exanthem, N/V

Photo Courtesy V.Lazareth NP

IV. Adnexal

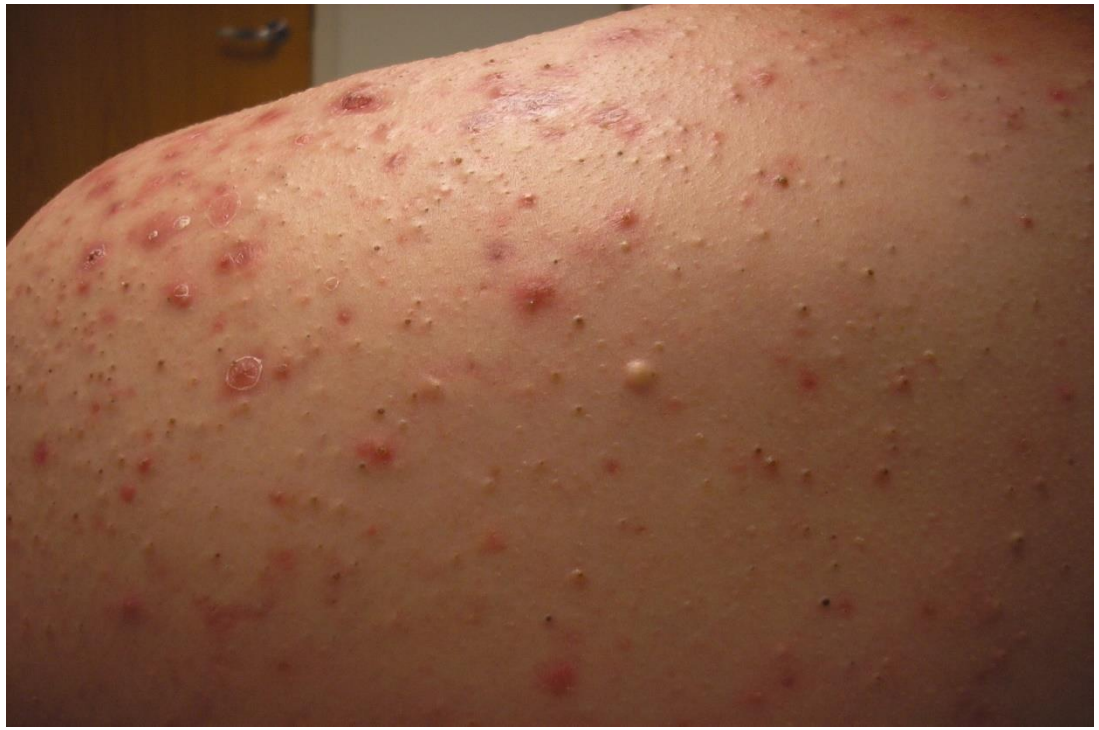


Photo Courtesy V.Lazareth NP

QUESTION 7

Your 15-year-old female pt has severe acne which has been unresponsive to conventional treatment. She is interested in isotretnoin and understands that it is contraindicated in women who may become pregnant. Her mother states that is not a problem as her daughter is already taking a progestin oral contraceptive pill.

Which of the following are *NOT* acceptable forms of birth control according to the iPLEDGE program?

A. tubal sterilization, partner's vasectomy, intrauterine device
B. hormonal (combination birth control pills, skin patches, shots, under-the-skin implants, or vaginal rings)
C. male latex condoms, diaphragm, cervical cap, or vaginal sponge, all with the co-use of spermicide
D. natural family planning, birth control pills without estrogen, female condoms, withdrawal, and cervical shield

isotretinoin: pt education

- isotretinoin is indicated for severe, resistant, nodular acne that is unresponsive to conventional therapy, including systemic antibiotics and acne scarring
- initial dose is 0.5 mg/kg/d then increased to 1.0 mg/kg/d for 15-20 weeks
- avoid esophageal irritation by taking isotretinoin with a full glass of water
- maximize absorption by taking isotretinoin with high-fat food
- avoid taking tetracyclines with isotretinoin (risk of benign intracranial hypertension)
- screen for the presence or development of depression, suicidal ideation and aggressive and/or violent behaviors prior to starting and while taking isotretinoin
- avoid blood donation while taking and for 1 month after discontinuing isotretinoin
- acceptable forms of birth control according to iPLEDGE include tubal sterilization, partner's vasectomy, intrauterine device, hormonal (combination birth control pills, skin patches, shots, under-the-skin implants, or vaginal rings), male latex condoms, diaphragm, cervical cap, or vaginal sponge, all with the co-use of spermicide

Photo Courtesy V.Lazareth NP

QUESTION 8

Your 29 yr old female pt Kara is a professional spin instructor who is increasingly frustrated with her persistent inflammatory acne. She has tried “every” topical without sustained improvement and is wary of isotretinoin. She currently takes Yaz OCP and has no plans for pregnancy. You consider spironolactone.

You explain to Kara that potential side effects of spironolactone include all *except*:

A. muscle cramps and weakness (hyperkalemia)
B. breast swelling and tenderness (gynecomastia)
C. menstrual dysfunction
D. palpitations, bloody nose (hypertension)

spironolactone

- FDA no Derm indications; diuretic. Off-label: acne
- well tolerated in women. AE: include dizziness, headaches, urinary frequency, muscle cramps, irregular menstruation, breast tenderness, and breast enlargement –particularly at higher doses. men are generally not prescribed spironolactone
- currently no evidence to support an increased risk of estrogen-sensitive cancers this in human subjects.
- 2015 study concluded that K+ monitoring is unnecessary for healthy young women
- Pregnancy Category C. Without the need for regular blood testing or the risk of severe teratogenicity, spironolactone is an attractive alternative to isotretinoin.

avoid potassium supplements including sports drinks due to the risk for hyperkalemia

Photo Courtesy V.Lazareth NP

Hidradenitis Suppurativa

- systemic antibiotics:
  minocycline or tetracycline 100 mg BID x 12 wks combination
  clindamycin and rifampin x 12 weeks
- metabolic therapy: metformin 1500 mg daily
  biguanide antihyperglycemic agent; reduces serum androgen, weight
  68% subjective improvement; 19% disease remission
- hormonal therapy: spironolactone 75-100 mg daily
  androgen receptor blocker; reduces steroid hormone binding
  less pain, fewer lesions. consider OCP, especially in PCOD
- Biologics FDA approved for HS
  with reduction in inflammatory nodules
  - (TNF-a): adalimumab (Humira®) ≥12 yr
  - (IL-17): secukinumab (Cosentyx®) (adult)

Photo Courtesy V.Lazareth NP

V. Systemic Immunosuppressive & Antiproliferative Drugs

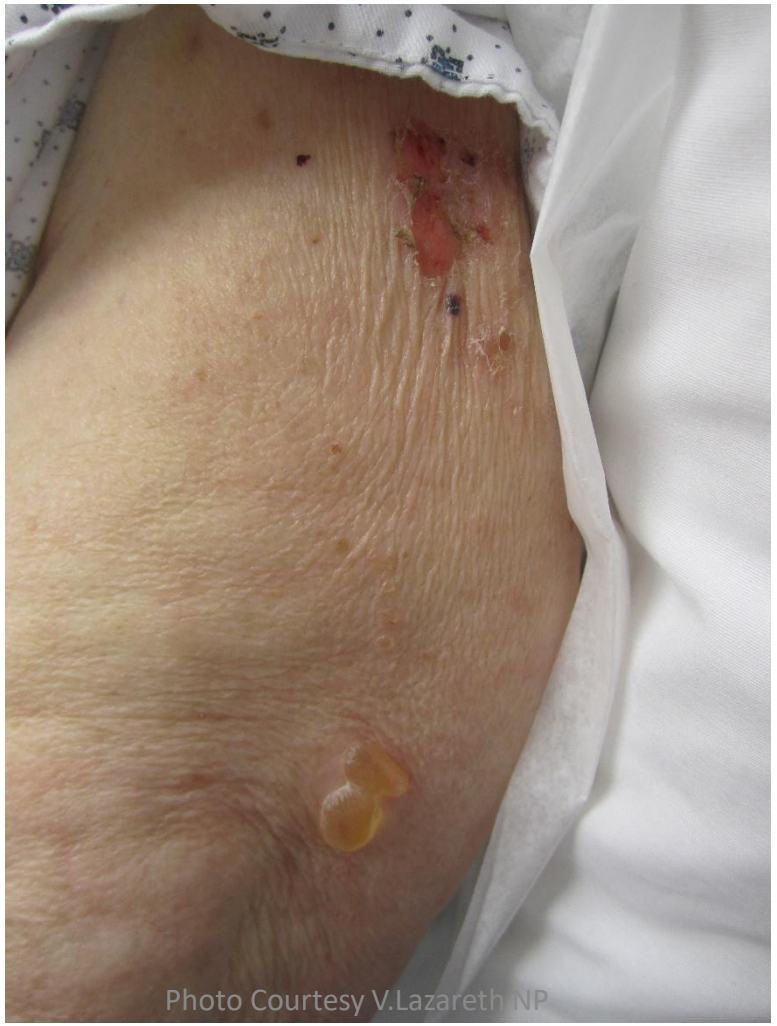


Photo Courtesy V.Lazareth NP

Question 9

A 53 yr female who has been under extraordinary stress was diagnosed 6 weeks ago with sudden onset, rapidly worsening, plaque psoriasis. She has a BSA of ~20%, is extremely itchy and unable to sleep. She failed UVA and developed vomiting and headaches with methotrexate. PMH: hysterectomy, depression.

You agree to proceed with biologic therapy with risankizumab, perform baseline lab work and submit the application for insurance coverage.

The pt returns in tears 3 days later requesting immediate relief. You consider:

A. apremilast

B. cyclosporine

C. acetretin

D. rituximab

Photo Courtesy V.Lazareth NP

cyclosporine

- In clinical trials, 80–90% of patients who took cyclosporine for 12–16 weeks experienced rapid relief from symptoms
- pts typically have a good remission period after stopping cyclosporine
- dermatologic dosage (3-5 mg/kg/d)
- CI: decreased kidney function, hypertension, immunosuppression, malignancy
- long-term safety data show no increased risk of opportunistic infections, tuberculosis reactivation, lymphoma or internal malignancies however, there is an increased risk of non-melanoma skin cancers (SCC)

Photo Courtesy V.Lazareth NP

Question 10

You are covering for a colleague who is on vacation. One of her pts, an 82 yr female with Pemphigus Vulgaris, has tolerated one month of prednisone therapy at 7.5 mg daily with improvement. Your colleague's notes indicate that she is planning to switch to a steroid-sparing agent after 3 months of treatment. You note that the pt has already had a baseline ophthalmologic exam, Chest x-ray and TB screening.

In the interim, which of the following should you monitor?

A. BP, Wt

B. BP, Wt, Glucose, electrolytes

C. BP, Wt, Glucose, electrolytes, glucose

D. BP, Wt, Glucose, electrolytes, glucose, hemoglobin

Photo Courtesy V.Lazareth NP

prednisone

Monitoring

- blood pressure, weight
- serum glucose, electrolytes, hemoglobin
- infections
- occult blood loss
- bone mineral density
- growth (pediatrics)
- HPA axis suppression (AM cortisol test, adrenocorticotropic hormone stimulation test, urinary free cortisol test)

Adverse Effects of Systemic Steroids

- Sick: immune suppression
- Sad: depression, mood changes
- Sex: decreased libido
- Salt: sodium retention, weight gain
- Sugar: elevated blood sugar

Photo Courtesy V.Lazareth NP

Question 11

A 75 yr male has been taking azathioprine to treat Bullous Pemphigoid. He states that he was recently started on a new medication by his PCP for hip pain. Reviewing his lab results at his 2-month follow-up visit you note a decrease of his WBC count to 2900/mm3 and of his hemoglobin level to 9 g/dl.

Which medication was most likely started?

A. allopurinol

B. colchicine

C. naproxen

D. prednisone

D. Allopurinol. Concomitant use of azathioprine and allopurinol increases the risk for bone marrow suppression. If azathioprine is given to pts on allopurinol, the dose must be markedly reduced.

azathioprine

- FDA: no Derm indications
- Off-Label: Immunobullous disease, Vasculitis, Atopic dermatitis, Connective Tissue Disease (SLE, dermatomyocytis)
- AEs: Immunosuppression, leukocytopenia, thrombocytopenia, N/V, opportunistic infection. (rare) pancytopenia, lymphoma, cSCC, female GU SCC.
- concomitant use of allopurinol increases the risk for bone marrow suppression
- concomitant use of cyclosporin or MTX increases the risk for a hypersensitivity reaction during the 1st mo
- BLACK BOX WARNING: chronic immunosuppression with azathioprine (a purine antimetabolite) increases the risk of post-transplant lymphoma and hepatosplenic T-cell lymphoma (HSTCL) in patients with IBD

Photo Courtesy V.Lazareth NP

mycophenolate mofetil

- FDA: no Derm indications
- Off-label: Bullous Pemphigus, Bullous Pemphigoid, Psoriasis
- Dosage: 2000 mg/day
- CI: Pregnancy, Lactation, PUD, Hepatic, Renal, Cardiopulmonary Disease
- increased toxicity: acyclovir
- decreased efficacy: cholestyramine, iron, aluminum, magneseum hydroxide
- Monitoring
  - CBC-diff, platelets, LFT monthly x 6 mo, then q 3-4 mo
  - if WBC <4000/mm2: decrease dose or D/C drug

Photo Courtesy V.Lazareth NP

VI. Oncodermatology

Photo Courtesy V.Lazareth NP

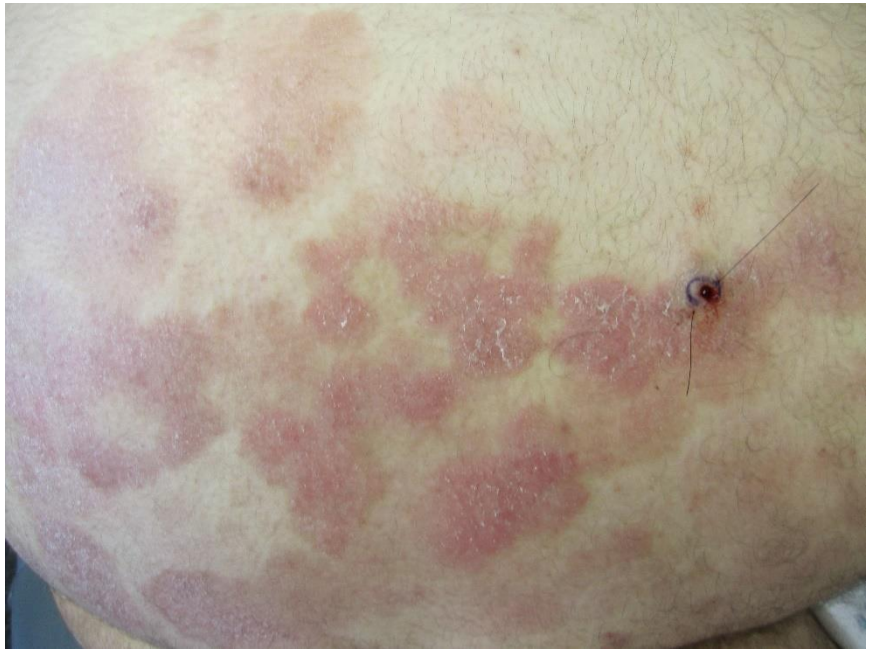
hydroxyurea

- FDA: anti-metabolite used for SCC of the head and neck, Metastatic Melanoma
- Off-label: psoriasis, hypereosinophilic syndrome, chronic myeloproliferative disorders
- CI: pregnancy, lactation, hypersensitivity, concomitant Ara-C, blood dyscrasia, infection, endocrine dysfunction, hepatic, renal or cardiac disease
- AE: Anemia, megaloblastic changes. Leukopenia, dermatomyositis-like lesions, flu-like syndrome (rare) leukemia, thrombocytopenia, hepatitis, malignancies, renal dysfunction, hyperpigmentation, leg ulcers, radiation recall
- Monitoring: CBC-diff, platelets, CMP, UA. weekly x 1 mo, then monthly, then q 3 mo
- decrease dose or D/C if reduction of Hb by 3 g/dl, WBC <3500 mm3, platelets <100,000/mm3, concomitant infection, organ system involvement

Photo Courtesy V.Lazareth NP

bexarotene

- FDA: Cutaneous T-cell Lymphoma
- systemic retinoid (vitamin A derivative) inhibits the growth of tumor cell lines and induces apoptosis of malignant lymphocytes
- Dose: 300 mg/m2 daily
- CI: teratogen: pregnancy, lactation
- AE: hyperlipidemia, hypothyroidism, hypercholesteremia, headache, asthenia (weakness), leukopenia, rash, nausea, infection, peripheral edema, abdominal pain, dry skin



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VII. Systemic Agents for Psoriasis

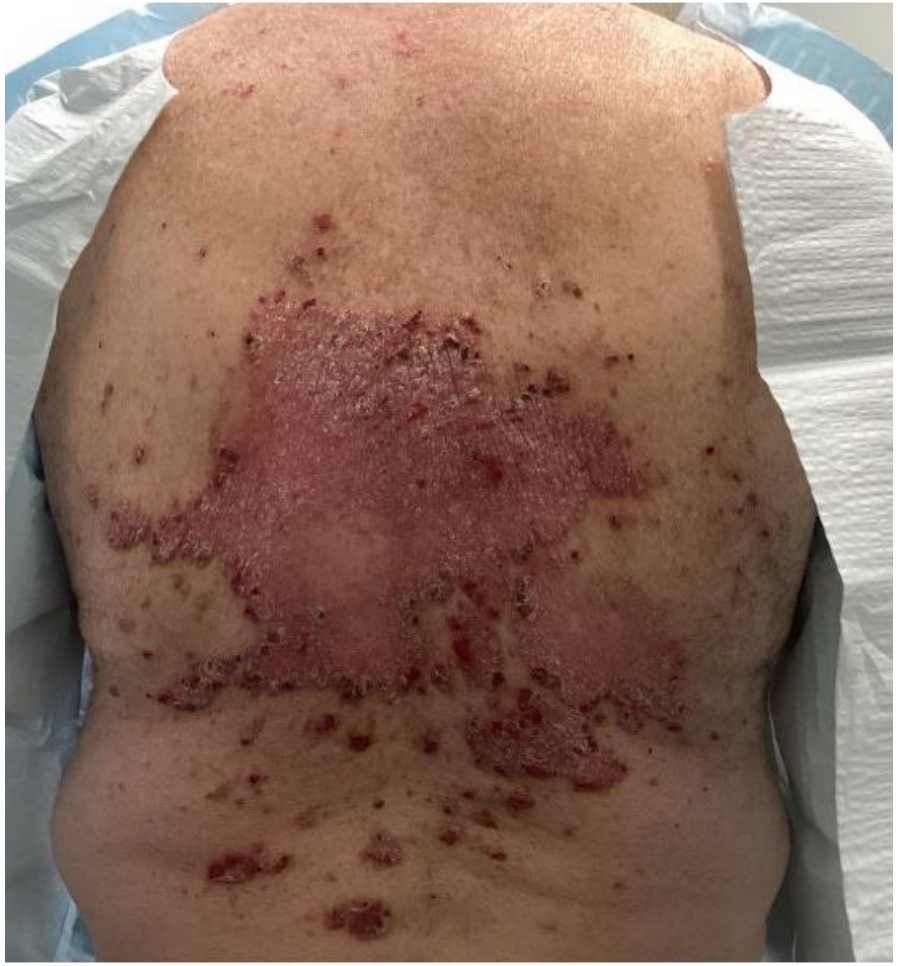


Photo Courtesy V.Lazareth NP

Systemic Agents for Psoriasis

- contributing factors to under-treatment of psoriasis include
  - pt concerns: adverse reactions, lab monitoring, injectable medications
  - provider concerns: adverse reactions, monitoring
- oral apremilast, phosphodiesterase-4 (PDE-4) inhibitor
  - reduces cytokine activation and inflammation
- oral deucravacitnib, TYK2 inhibitor, a 1st in class therapy
  - prevent signaling from IL-12 and IL-23 which activate the Th17 cells that drive PS
- may be options for pts who do not want to use an injectable medication

Photo Courtesy V.Lazareth NP

apremilast

apremilast 30 mg BID tabs

- phosphodiesterase-4 (PDE-4) inhibitor which reduces cytokine activation and inflammation
- I: plaque, scalp, palmoplantar PS and PsA
  - Scalp PS 4x the risk of developing PsA
- CI: pregnancy, lactation. depression, Crohn's, IBD
- AE: diarrhea, nausea, URI, HA, wt loss, mood changes, depression, suicidal ideation
- Efficacy: 33% clearer skin, 46% reduction in itch

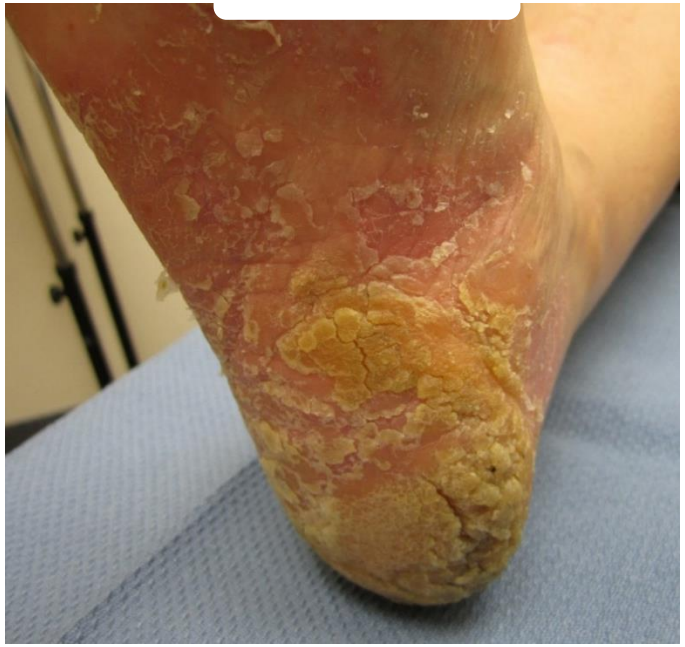


Photo Courtesy V.Lazareth NP

deucravacitinib

deucravacitinib IL-23 inhibitor

- TYK2 Janus Kinase family of cytokines
- once-daily 6 mg oral treatment for moderate-severe PsO
- Efficacy
  - 55% clear/ almost clear with deucravacitinib vs 32% apremilast
  - 74% PASI-75 in deucravacitinib vs 38% apremilast in POETIC PSO1 & 2
- CI: pregnancy, lactation, concomitant immunosuppressants
- AE: nasopharyngitis, URI, headache, diarrhea, nausea, HSV-HZV reactivation
- Monitoring: Q Gold, Hepatitis B+C, Lipids. Routine annual labs. vaccines.

Photo Courtesy V.Lazareth NP

VIII. Biologics for Atopic Dermatitis

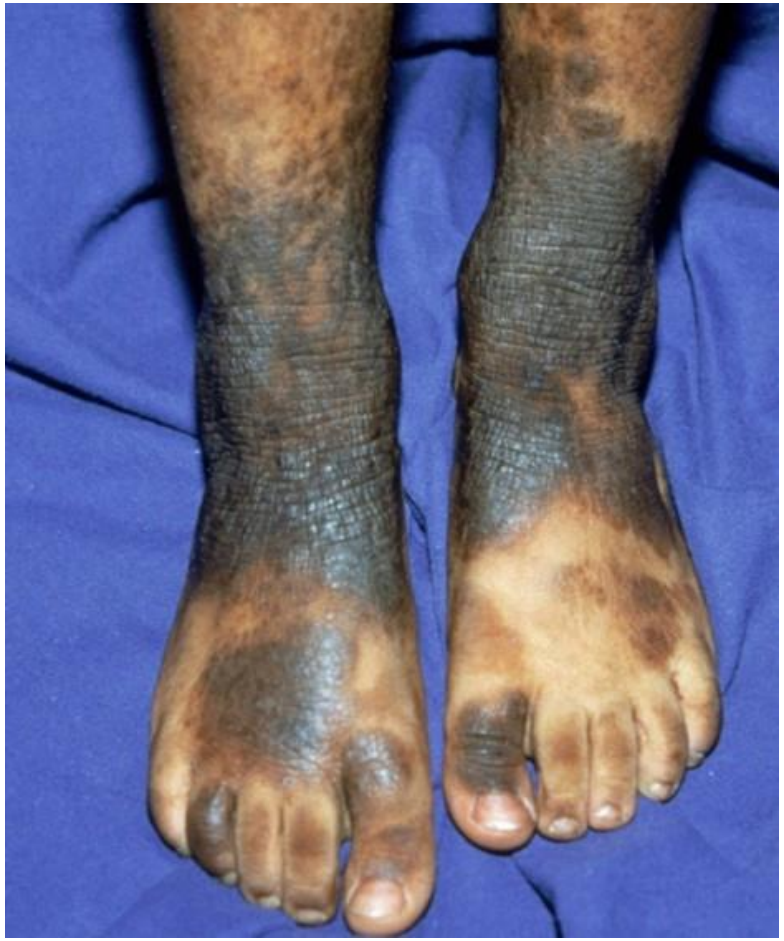


Photo Courtesy V.Lazareth NP

Biologics

- Biological products are isolated from a variety of natural sources
- vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins
- can be sugars, proteins, nucleic acids or a complex combination
- can be used to treat a variety of diseases (immune-related diseases; rheumatoid arthritis, psoriasis, Crohn's Disease)
- interrupt signals and pathways in the immune system to reduce the damage inflicted by these diseases; Insulin, Botox, Humira and Rituxan
- Atopic dermatitis is a chronic inflammatory disease with a complex pathogenesis and heterogeneous clinical presentation
- multiple advanced therapies approved for the treatment of moderate-severe AD include the biologics dupilumab, tralokinumab, and lebrikizumab

Photo Courtesy V.Lazareth NP

dupilumab

dupilumab IL-4, IL-13 Inhibitor

- I: moderate-severe Atopic Dermatitis >6 mo, Prurigo Nodularis >18 yr
- I: asthma >6 yr, chronic rhinosinusitis >18 yr, eosinophilic esophagitis 12 yr
- Monitoring: no requirement for lab monitoring
- Dose: 600 mg loading, then 300 mg SC q 2 wks (modified dosing for cld & ado)
- AEs: conjunctivitis, keratitis, blepharitis, eye pruritis, dry eye, HSV, injection site reactions, hypersensitivity, helminth/parasitic infections
- LIBERTY AD SOLO 1 and 2
  - 36-38% achieved clear/almost-clear; >60% EASI-75 at 1 yr
  - reductions in daily itch, improved sleep and quality of life were also observed

tralokinumab

tralokinumab IL-13 inhibitor

- moderate-severe AD in pts ≥12 yr whose disease is not adequately controlled with topical Rx therapies or when those therapies are not advisable
- Dosing: initial 600 mg dose then 300mg every other wk
- consider 300 mg q 4 wks for pts <220 lbs who achieve clear/ almost clear
- AEs: URIs, conjuctivitis, keratitis, injection site reactions, eosinophilia
- Warnings: hypersensitivity, parasitic infection, risk of infection with live vaccines
- ECZTRA 1 and 2
  - 15/22% achieved clear/almost clear; on tralokinumab vs 7/10% on placebo
  - reduction in daily worst itch rating, improved sleep and quality of life

Photo Courtesy V.Lazareth NP

lebrikizumab

lebrikizumab IL-13 inhibitor

- human monoclonal antibody FDA approved for the treatment of pts ≥12 years ≥40 kg with moderate-to-severe atopic dermatitis that has not been adequately controlled using topicals
- In an average of two studies (ADvocate 1 and 2), 38 percent of people who took EBGLYSS achieved clear or almost-clear skin at 16 weeks
- 77% maintained those results at one year with once-monthly dosing.
- 43% felt itch relief at 16 weeks
- 85% still felt that relief at 1 year of treatment with monthly maintenance dosing
- AE: injection site reactions, dry eye and conjunctivitis (redness and discomfort in the eye) including allergic conjunctivitis and herpes zoster

Photo Courtesy V.Lazareth NP

IX. Biologics for Psoriasis

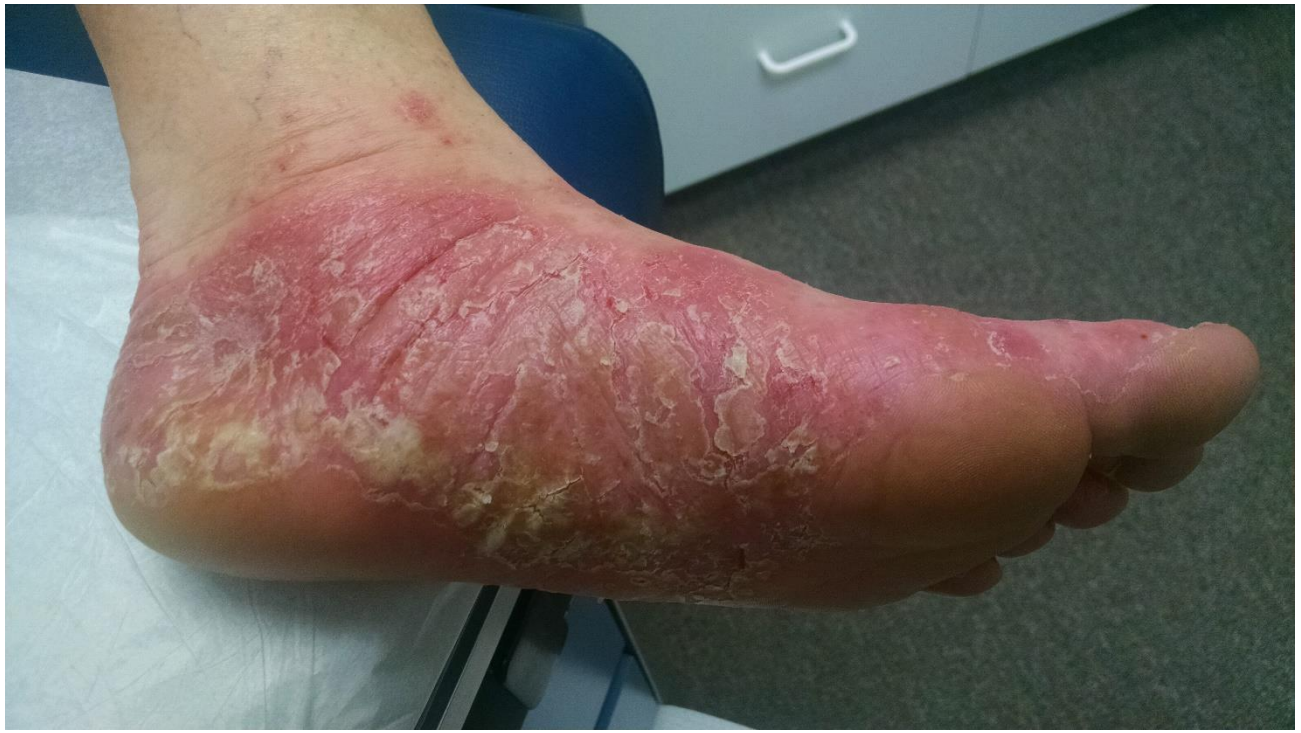


Photo Courtesy V.Lazareth NP

TNF-*a* inhibitors:
adalimumab, etanercept, certolizumab

adalimumab (adult), certolizumab (adult), etanercept (≥4 yr): TNF-*a* inhibitors

FDA	**psoriasis, psoriatic arthritis**
	adalimumab: hidradenitis suppurativa
	certolizumab: preferred biologic for psoriasis in pregnancy
CI	hypersensitivity, active, chronic, localized infection Relative contraind: PMH/FMH of demyelinating diseases
AEs	upper respiratory, sinusitis, injection site reactions, headache, rash (rare) CNS peripheral demyelinating dz, pancytopenia, CHF, lupus-like syndrome
Labs	baseline: TB, HIV, Hep B, Hep C, CBC, CMP, LFT CBC, CMP, LFT at 3 mo, then q 6-12 m. annual TB

Increased risk for serious infection, lymphoma, BCC, SCC, hepatitis B reactivation

Photo Courtesy V.Lazareth NP

IL-12/23 inhibitor:
ustekinumab

ustekinumab (≥6 yr) IL-12/23 inhibitor

- targeted antibody
- FDA approval: **psoriasis, psoriatic arthritis**
- PHOENIX 1: 59% - 61% assessed as clear/near clear
- PHOENIX 2: PASI 75 achieved by 67% - 76%
- CI: active infection (mycobacteria, salmonella), live vaccines (especially BCG), concomitant methotrexate, prednisone
- AEs: nasopharyngitis, URI, headache, fatigue
- Monitoring:
  baseline: TB, HIV, Hep B, Hep C, CBC, CMP, LFT.
  CBC, CMP, LFT q 6-12 mo. annual TB

Photo Courtesy V.Lazareth NP

IL-23 inhibitors:

risankizumab, guselkumab, tildrakizumab

risankizumab (adult), guselkumab (adult), tildrakizumab (adult) IL-23 inhibitors

- FDA: **psoriasis, nail psoriasis, pustular psoriasis, erythroderma**
- In clinical trials, risankizumab showed rapid improvements in skin clearance
  - 75% of pts saw a 90% improvement in 4 mo
  - at one year, nearly 60% of patients achieved 100% clear skin
- RESURFACE: 74% achieved PASI 75 clearance at week 28 with tildrakizumab
- Dosage: 150 mg wk 0 & wk 4, then q 12 wks
- CI: infections, live vaccines, concomitant methotrexate and prednisone
- AE: risankizumab, tildrakizumab: URI. guselkumab: flu-like illness
- Monitoring: TB, HIV, Hep B, Hep C, CBC, CMP, LFT. annual TB

Photo Courtesy V.Lazareth NP

IL-17 Inhibitors:
bimekizumab, ixekizumab, brodalimumab, secukinumab

ixekizumab (≥6 yr), secukinumab (≥6 yr), bimekizumab (adult), brodalimumab (adult)

- IL-17 inhibitors
- ixekizumab: 40% achieved 100% clear skin at 12 weeks
- secukinumab: 45% achieved 100% clear skin at 16 weeks. (approved for H.S. ≥12 yr)
- bimekizumab: 62% achieved 100% clear skin at 16 weeks
- brodalimumab: carries a warning for suicidal ideation and behavior
- CI: IBD, Crohn's, Hypersensitivity, concomitant Methotrexate, Prednisone
- AEs: IBD, Serious Infections, MS & CT Disorders, Allergic, Malignancies, HTN, CV Event, Injection Site, Nasopharyngitis, URI, Oropharyngeal Pain, Pruritus, Back Pain, Eczema, Nausea, Diarrhea, Urticarial, Tinea
- Monitoring: TB, HIV, Hep B, Hep C, CBC, CMP, LFT. annual

X. Janus Kinase Inhibitors: Atopic Dermatitis

Photo Courtesy V.Lazareth NP

JAKs for AD

- Atopic dermatitis (AD) is a chronic inflammatory disease with a complex pathogenesis and heterogeneous clinical presentation
- multiple advanced therapies are approved for the treatment of moderate-severe AD, including the biologics dupilumab, tralokinumab, and lebrikizumab and the oral Janus kinase inhibitors abrocitinib, upadacitinib, and baricitinib
- Biologic and JAK treatments have different efficacy, safety, and tolerability profiles and monitoring requirements
- important aspects to consider include treatment goals, medical history, symptom severity, physician assessments, safety profile of drugs, and pt preference

Samynathan A, Silverberg JI. Navigating the atopic dermatitis toolbox: Challenging scenarios and shared decision-making. Ann Allergy Asthma Immunol. 2024 Mar;132(3):337-343. doi: 10.1016/j.anai.2023.12.020. Epub 2023 Dec 23. PMID: 38145707.

Photo Courtesy V.Lazareth NP

Question 12

- 29 yr old male returns with complaints of persistently itchy areas of skin at his arms, legs, face and neck
- He has had eczema since childhood which waxes and wanes but never resolves. He has used multiple TCS, TCI and prednisone.
- You have prescribed a course of crisaborole (Eucrisa) ointment BID but it has not been effective. At this point he is frustrated with creams but admits to being fearful of injections.
- Which treatment would you consider next?

abrocitinib (Cibinqo) po systemic JAK1 inhibitor: requires some monitoring
upadacitinib (Rinvoq) po systemic JAK1 inhibitor: requires some monitoring

Photo Courtesy V.Lazareth NP

Janus Kinase (JAK) Inhibition

- Janus kinases are key drivers of cytokine signaling and inflammatory response
- cytokines bind to cell surface receptors, activate JAK-STAT pathway, form a dimer that enters nucleus and binds to DNA, targeting gene transcription to form more cytokines
- JAK inhibitors (JAK1, JAK2, JAK3, TYK2) are small molecules that modulate cytokine signaling inhibiting the inflammatory response
  - JAK-STAT pathway mediates signaling of IL-4, IL-5, IL-13, IL-31 in *acute* AD; and mediates T helper (Th1, Th17, Th22) cytokines in *chronic* AD
  - JAK1, JAK2 and TYK2 impact IL-13 (pruritus, skin barrier dysfunction, skin bacteria composition, and immune abnormalities in AD)

Photo Courtesy V.Lazareth NP

Janus Kinase Inhibitors: upadacitinib

upadacitinib JAK1 Inhibitor

- I: pts ≥12 yr with refractory, moderate-severe AD whose disease is not adequately controlled with other systemic drugs, including biologics
- Dosing: >12 yr, >40 kg, >65 yr, renal imp: 15 mg po daily; (adults up to 30 mg daily)

Measure Up 1 & 2, AD Up:

- 60-80% achieved (Eczema Area and Severity Index) EASI-75
- all showed significant improvement in Itch
- AEs: nausea, cough, fever, acne, headache.
  increased CPK-lipids-LFTs-wt, neutropenia, lymphopenia, allergic reactions, folliculitis, abd pain, fatigue, muscle pain, flu-like illness, rash, retinal detachment

Janus Kinase Inhibitors: abrocitinib

abrocitinib JAK 1 inhibitor

- I: pts ≥12 yr with refractory, moderate-severe AD whose disease is not adequately controlled with other systemic drugs, including biologics
- CI: antiplatelet therapies (except low-dose ASA) during first 3 mo of treatment
- Dosing: 100 mg daily (up to 200 mg daily)
- AEs: nasopharyngitis, nausea, headache. HSV, increased CPK, dizziness, UTI, fatigue, acne, vomiting, oropharyngeal pain, influenza, gastroenteritis, impetigo, HTN, contact dermatitis, upper abd pain, HZV, thrombocytopenia, retinal detachment
- JADE MONO-1, JADE MONO-2: 40-68% Eczema Area and Severity Index (EASI-75)

Photo Courtesy V.Lazareth NP

JAK Inhibitors

- RA trial of tofacitinib reported major CV events and malignancies in pts >50
- Black Box Warnings for all JAK Inhibitors
  - higher rate of all-cause mortality
  - higher rate of MACE events (CV death, MI, stroke)
  - thrombosis (DVT, PE, arterial)
  - serious infections
  - lymphoma, other malignancies
- Contraindications
  - hypersensitivity, GI perforation, concomitant prednisone, MTX, live vaccines (Shingles prior to start)
  - CV risk, hx of cancer, immunosuppression, pregnancy, lactation, <12 yr
- Lab monitoring
  - Hepatitis B&C, Q-Gold, HCG
  - CBC-diff, LFTs (at baseline and after initiation or dose-escalation)
  - Lipids 3 m after initiation

Drug Safety in Pregnancy

- systemic antihistamines
  - (pruritus, urticaria) chlorpheniramine, diphenhydramine and 2nd generation antihistamines are preferred
- systemic acne drugs
  - avoid isotretinoin, spironolactone
- systemic antifungals
  - avoid fluconazole, ketoconazole, itraconazole
- systemic antibiotics
  - amoxicillin, 1st generation cephalosporins, clindamycin, dicloxicillin: safe
  - rifampin (TB): preferred. Avoid trimethoprim, sulfonamide, quinolone, tetracycline
- systemic PDE4
  - apremilast: should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, caution in lactation

Truong, Thu Minh PharmD1; Yaghi, Marita MD2; Murase, Jenny MD3,4. Dermatologic Drug Safety in Pregnancy. Journal of Dermatology for Physician Assistants 17(3):p 1-12, Summer 2023. | DOI: 10.58744/001c.88954

Photo Courtesy V.Lazareth NP

Drug Safety in Pregnancy

- systemic biologics
  - PS: certolizumab pegol or etanercept which have minimal placental transfer should be favored
  - AD: dupilumab unknown risk
- systemic steroid
  - assoc lower fetal gestational age and lower birth weight
  - slight increase in malformations, esp cleft palate
  - prednisone preferred over betamethasone and dexamethasone
- systemic Janus Kinase inhibitors
  - avoid in pregnancy and lactation and for 4 wks after last dose
  - deucravacitinib (TYK2): not assoc with increased rates of fetal loss or malformations
- systemic immunosuppressants
  - avoid: azathioprone, cyclosporin, mycophenolate mofetil

Truong, Thu Minh PharmD1; Yaghi, Marita MD2; Murase, Jenny MD3,4. Dermatologic Drug Safety in Pregnancy. Journal of Dermatology for Physician Assistants 17(3):p 1-12, Summer 2023. | DOI: 10.58744/001c.88954

Photo Courtesy V.Lazareth NP

Drug Safety in Pregnancy

- Avoid
  - PUVA
  - systemic antifungals
  - minoxidil (topical+systemic)
  - topical clascoterone
  - roflumilast during labor & delivery
- Preferred systemics
  - 2nd gen antihistamines
  - acyclovir
  - certolizumab pegol
- Preferred topicals
  - salicylic acid
  - permetherin

Truong, Thu Minh PharmD1; Yaghi, Marita MD2; Murase, Jenny MD3,4. Dermatologic Drug Safety in Pregnancy. Journal of Dermatology for Physician Assistants 17(3):p 1-12, Summer 2023. | DOI: 10.58744/001c.88954

Photo Courtesy V.Lazareth NP

III. Drug Reactions

Photo Courtesy V.Lazareth NP

Case Study

79F c/o itchy rash

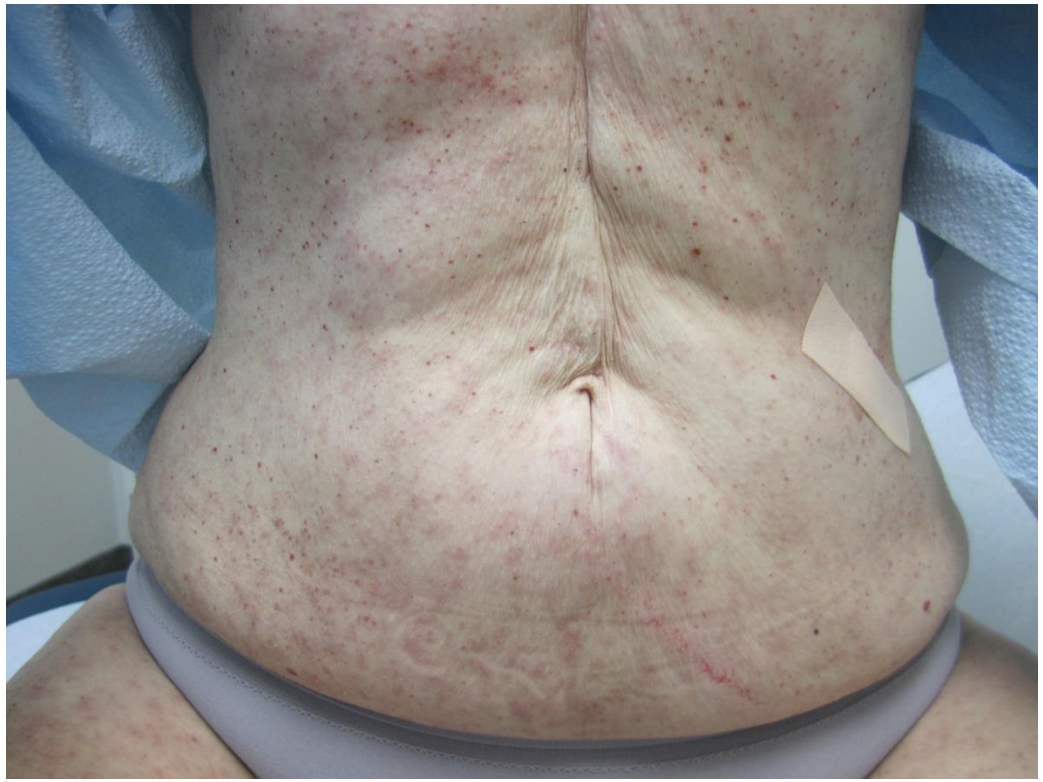


Photo Courtesy V.Lazareth NP

Case Study

31

- Amoxicillin 500 MG Cap
- Hydrochlorothiazide 12.5 MG Cap
- Sertraline 50 MG Tab
- Diltiazem 120 MG Capsule SR 24 Hr
- Levothyroxine 137 MCG Tab
- Trazodone 50 MG Tab
- Mesalamine (Pentasa) 500 MG Cap CR
- Rivaroxaban (Xarelto) 20 MG Tab
- Pregabalin (Lyrica) 25 MG Cap
- Dicyclomine 10 MG Cap
- Acetaminophen 500 MG Tab
- Cyclobenzaprine (Flexaril) (muscle spasms)
- Preparation H 0.25-14-74.9 % Oint (hemorrhoids)
- Albuterol (2.5 MG/3ML) 0.083% Nebu Soln (asthma)
- Ventolin HFA 108 (90 Base) MCG/ACT Aero Soln (asthma)
- Valacyclovir 1 GM Tab (HSV)

- Biotin 2.5 MG Tab
- Nystatin 100000 UNIT/GM Powder
- Oxybutynin (Ditropan) 5 MG Tablet SR 24 Hr
- Pantoprazole Sodium (Protonix) 20 MG Tablet Delayed Response
- Diclofenac Sodium 1 % Gel
- Atorvastatin 10 MG Tab
- Fluticasone 50 MCG/ACT Suspension
- Cholecalciferol (VITAMIN D PO)
- Probiotic Product (PRO-BIOTIC BLEND) CAPS
- Zyrtec daily
- Senna daily
- Fish Oil daily
- Iron daily
- Visine eye drops
- Saline Nasal Spray
- Cranberry tablets (juice)
- Potassium tablets (daily shakes with fruits, spinach, kale)
- Calcium (lactose-free milk)
- Benadryl (Sarna anti-itch solution)

Photo Courtesy V.Lazareth NP

Adverse Cutaneous Drug Reactions

Unintended toxic response to a drug

- fatal to ~100,000 US pts annually
- a drug may be taken for *years* prior to a reaction
- most common drugs:
  - aminopenicillins
  - sulfonamides
  - NSAIDs

History

- Instill (eye, ear drops, contact lens solution
- Ingest (capsules, tabs, gels, liquids)
- Inhale (corticosteroids)
- Inject (IM, IV, SC)
- Insert (suppositories)
- Intermittent (not taken every day)
- In secret (sharing among elders or teens)

Photo Courtesy V.Lazareth NP

Factors which predispose pts to a drug reaction

Pt characteristics

- hx of an ACDR, polypharmacy, elderly, children, F>M
- immune suppression, malignancies (lymphoma)
- certain Human Leukocyte Antigen proteins (HLA) types (phenytoin, carbamazepine, allopurinol, sulfamethoxazole, abacavir)

the drug itself

- class of drug, dose, route of administration, drug–drug interactions

viral illness

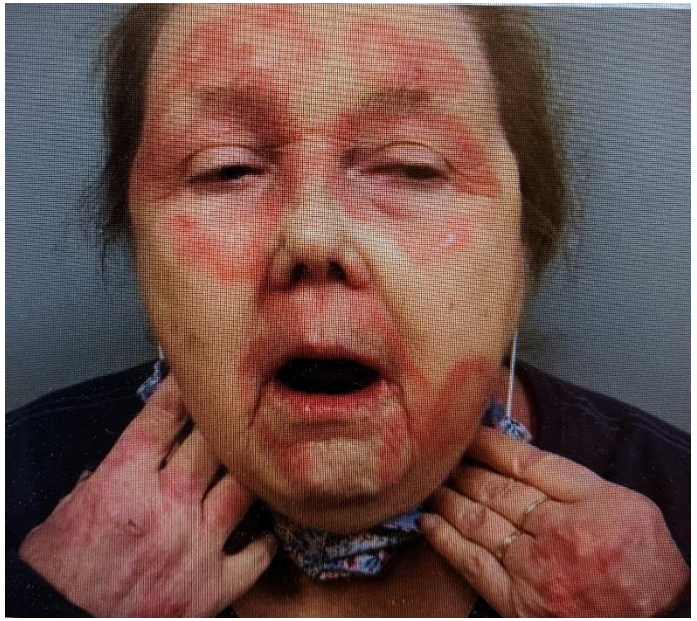
- ampicillin-induced rash with Epstein–Barr virus;
- trimethoprim-sulfamethoxazole–induced rash with HIV)

Photo Courtesy V.Lazareth NP

Clinical Presentation

Assessment for systemic involvement

- pruritic, bilateral, symmetrical, generalized
- linear, annular, grouped
- non-blanching (think vasculitis)
- oral or genital involvement
- lymphadenopathy, systemic symptoms



Red Flag signs and symptoms of systemic involvement:

- facial edema, angioedema, erythroderma, purpura
- blisters (+Nikolsky sign), necrosis or erosions of mucous membranes
- lymphadenopathy, fever, arthralgia, dyspnea, chest pain
- meningism (headache, neck stiffness, photophobia, nausea, vomiting)

Photo Courtesy V.Lazareth NP

Diagnostics

- Punch skin biopsy for histopathology (H&E)
  - histology can support the diagnosis but
  - a skin biopsy cannot identify offending agent!
- Punch skin biopsy for direct immunofluorescence (DIF)
  - obtain a 2nd punch biopsy in Michel's medium for DIF
  - if connective tissue disease or autoimmune blistering disease suspected
- Lab studies (in pts with systemic symptoms)
  - CBC-diff, CMP
  - Antinuclear antibody screening (ANA)
  - Antihistone antibodies (drug-induced lupus)
  - Blood cultures, bacterial cultures, viral cultures, urinalysis, stool guaiac (infection, vasculitis)

Photo Courtesy V.Lazareth NP

Approach to Pt with Suspected Drug Eruption

- Discontinue the offending drug
- Pt education: instruct pts to notify health care provider if:
  - rash recurs or worsens (severe hypersensitivity reaction)
  - fever develops or redness starts to spread over the body
  - blisters, ulcerations, or sores on any mucous membrane
  - new onset of pain
  - stridor, tongue swelling, shortness of breath
  - lifelong avoidance of the offending drug, meds in the same class, and any other classes with cross-reactivity
- Refer pt to the ER if systemic involvement is suspected

Photo Courtesy V.Lazareth NP

Case Study

11

- Amoxicillin 500 MG Cap
- Hydrochlorothiazide 12.5 MG Cap
- Sertraline 50 MG Tab
- Diltiazem 120 MG Capsule SR 24 Hr
- Levothyroxine 137 MCG Tab
- Trazodone 50 MG Tab
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- Pregabalin (Lyrica) 25 MG Cap
- Dicyclomine 10 MG Cap
- Acetaminophen 500 MG Tab

PRN:

- Cyclobenzaprine (Flexaril) (muscle spasms)
- Preparation H 0.25-14-74.9 % Oint (hemorrhoids)
- Albuterol (2.5 MG/3ML) 0.083% Nebu Soln (asthma)
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- ~~Biotin 2.5 MG Tab~~
- ~~Nystatin 100000 UNIT/GM Powder~~
- ~~Oxybutynin (Ditropan) 5 MG Tablet SR 24 Hr~~
- ~~Pantoprazole Sodium (Protonix) 20 MG Tablet Delayed Response~~
- ~~Diclofenac Sodium 1 % Gel~~
- ~~Atorvastatin 10 MG Tab~~
- ~~Fluticasone 50 MCG/ACT Suspension~~
- ~~Cholecalciferol (VITAMIN D PO)~~
- ~~Probiotic Product (PRO-BIOTIC BLEND) CAPS~~
- ~~Zyrtec daily~~
- ~~Senna daily~~
- ~~Fish Oil daily~~
- ~~Iron daily~~
- ~~Visine eye drops~~
- ~~Saline Nasal Spray~~
- ~~Cranberry tablets~~ (juice)
- ~~Potassium tablets~~ (daily shakes with fruits, spinach, kale)
- ~~Calcium~~ (lactose-free milk)
- ~~Benadryl~~ (Sarna anti-itch solution)

Photo Courtesy V.Lazareth NP

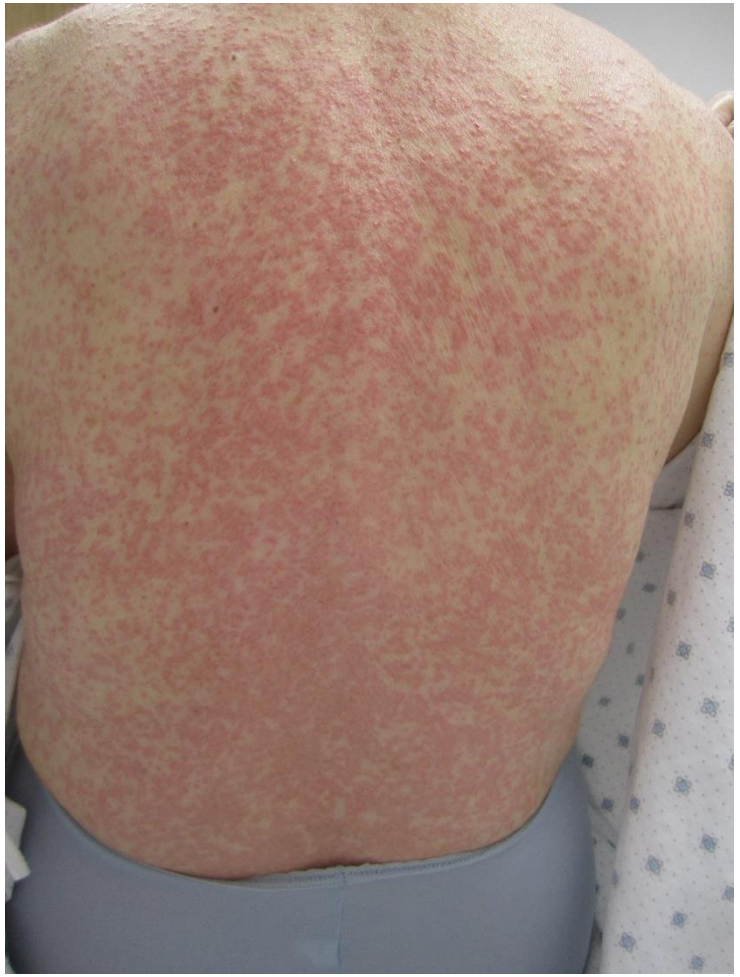
Common Drug Reaction Patterns

Photo Courtesy V.Lazareth NP

Erythematous Drug Eruptions

- ~95% of all ACDRs present as erythematous drug reactions
- onset is within *hours to weeks* after exposure; usually within 7-10 days and lasts 1-2 wks
- Itchy morbiliform (measles-like) red macules and papules in confluent symmetric, generalized distribution

Allopurinol, Amoxicillin, Ampicillin, Barbiturates, Cephalosporins, Captopril, Carbamazepine, Chlorpromazine, Diflunisal, Enalapril, Gentamycin, Gold, Glipizide, Glyburide, Isoniazid, Lithium, Naproxen, Penicillin, Phenothiazines, Phenylbutazone, Phenytoin, Piroxicam, Quinidine, Sulfonamides, Thiazides, Thiouracil, TMP/SMX



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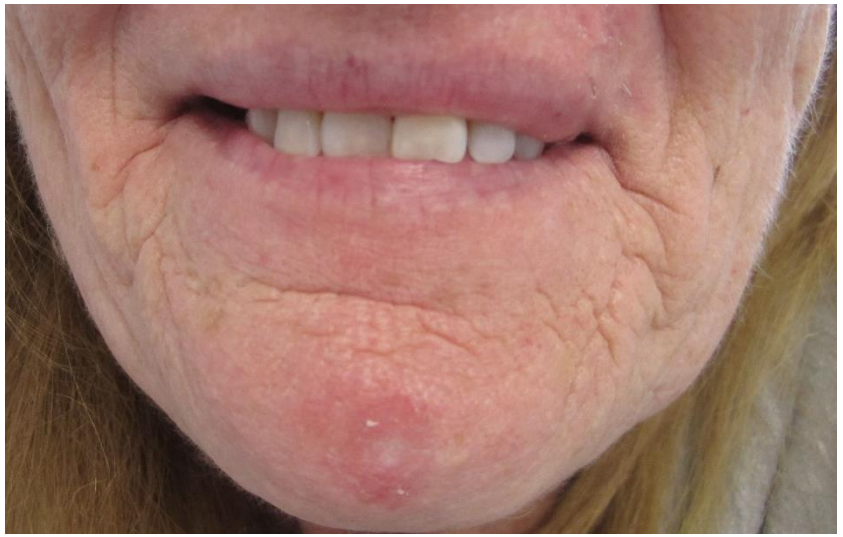
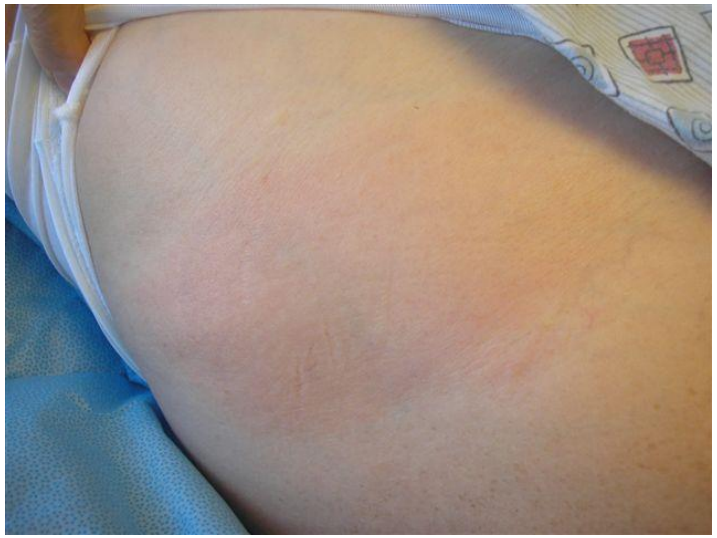
Other Drug Reaction Patterns

Fixed Drug Reaction



antibiotics, allopurinol, barbiturates, griseofulvin, NSAIDs, phenolphthalein-containing laxatives, propranolol, food dyes

Urticaria and angioedema



(peanuts, pollen, bee stings, blood transfusions)
6% drugs: ACE inhibitors, penicillin, aspirin, ibuprofen, naproxen

Photo Courtesy V.Lazareth NP

Adverse Cutaneous Drug Eruptions

Photo Courtesy V.Lazareth NP

Generalized Exfoliative Dermatitis (Erythroderma)

- potentially life-threatening disease from drugs:
- also from flares of pityriasis rubra pilaris, psoriasis, cutaneous T-cell lymphoma
- generalized erythema and desquamation
- lymphadenopathy, hepatosplenomegaly
- leukocytosis, eosinophilia, anemia

allopurinol, animalarials, arsenicals, barbiturates, captopril, cefoxitin, chloroquine, cimetidine, codeine, gold salts, hydantoins, isoniazid, lithium, nsaids, pcn, phenothiazines, phenytoin, sulfonamides, sulfonylureas

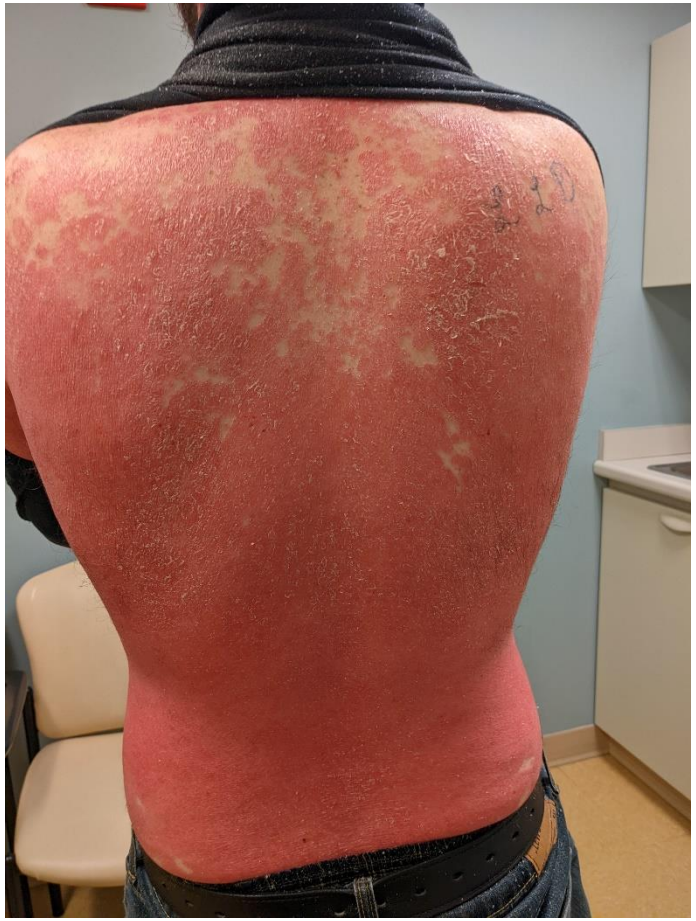


Photo Courtesy V.Lazareth NP

Erythema Multiforme

- acute onset of round, erythematous, edematous target lesions
- symmetrical extensor extremities; spread to trunk, neck, face
- EM major: severe mucosal erosions and systemic symptoms
- EM minor: no mucosal erosions or systemic symptoms
- 90% associated with infections:
  - HSV; also EBV, bacteria (*M pneumoniae),* dermatophytes
- 10% with drugs:
  - antibiotics, antiepileptics, NSAIDs, sulfonamides

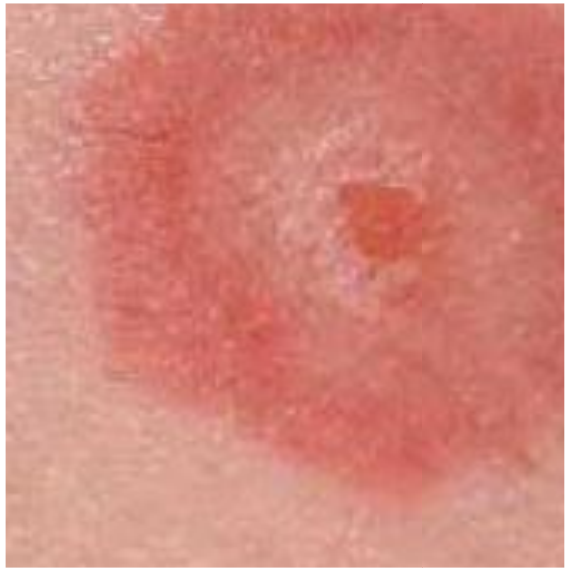
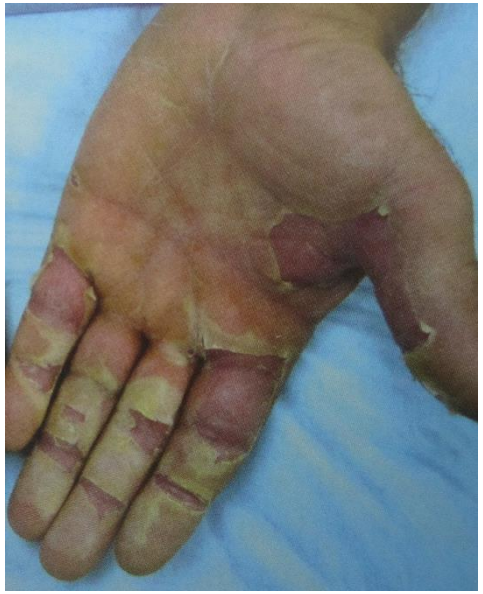


Photo Courtesy V.Lazareth NP

Stevens Johnson Syndrome & Toxic Epidermal Necrolysis

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

- rare medical emergencies with high morbidity and mortality
- full-thickness desquamation of cutaneous and mucosal surfaces
- fluid-electrolyte imbalance, infections
- 10-15% mortality for SJS; 30-40% mortality for TEN



Toxic Epidermal Necrolysis

- drugs are more often implicated than in SJS
- inherited defect in detoxification of drug metabolites

Photo Courtesy V.Lazareth NP

Stevens Johnson Syndrome & Toxic Epidermal Necrolysis

Drugs	Infections
allopurinol abx (penicillins, cephalosporins, quinolones, sulfonamides) amithiozone (thioacetazone) antiretrovirals (nevirapine, efavirenz, etravirine) barbiturates biologics (rituximab, cetuximab) carbamazepine checkpoint inhibitors (ipilimumab, nivolumub) chlormezanone phenytoin anticonvulsants lamotrigine (co-administered with valproic acid) phenylbutazone piroxicam	Mycoplasma Cytomegalovirus Cocksackie virus Herpes simplex Mumps Epstein–Barr Streptococcus

Photo Courtesy V.Lazareth NP

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Adverse Cutaneous Drug Eruptions

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