## Overview

- Inflammatory Diseases of the skin: Acne, Rosacea, Psoriasis, Atopic Dermatitis
- Infections: Zoster, Zika
- Pre-malignant and malignant neoplasms: Actinic Keratoses, Basal Cell Carcinoma, Squamous Cell Carcinoma, Melanoma

## Pathogenesis of Acne Vulgaris

- Sebum production by the sebaceous gland
- *P. acnes* follicular colonization
- Alteration in the keratinization process
- Release of inflammatory mediators into the skin, i.e. role of sebaceous lipids and inflammatory mediators including MMPs.

# Treatment of Acne

## Why treating acne and rashes is getting so expensive

JAMA Dermatology

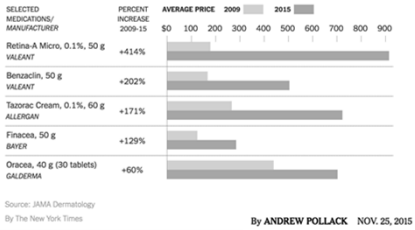
U.S.News & World Report HEALTH

The Washington Post

The New York Times

**Rising Prices for Acne Drugs**

The average prices of many common medications for acne or rosacea have risen sharply since 2009. Two of those that rose most were Valeant's Benzaclin and Retin-A Micro.




Source: JAMA Dermatology
By The New York Times

By ANDREW POLLACK NOV. 25, 2015

## Comedonal Acne Treatment

**Comedolytic Agents**

Topical Retinoids
Topical Azelaic Acid
(also antibacterial)
Topical Salicylic Acid

- Corrects keratinization in the follicle

## Mild Inflammatory Acne Treatment

- Benzoyl peroxide
- Sodium Sulfacetamide +/- sulfur
- Topical Antibiotics
- Azelax [Azelaic Acid] 20% Cream

## Mild Inflammatory Acne

**Topical Antibiotics**

- **Clindamycin** and **Erythromycin**
- If used alone resistance is common
- Dapsone gel

## Moderate Inflammatory Acne

- **Oral Antibiotics**
- Antibacterial (decrease in P. acnes)
- Anti-inflammatory (decrease in free fatty acids)
- Limit to 3 months

## Moderate Inflammatory Acne Treatment

**Oral antibiotics**

- **Tetracycline** 250mg-500mg BID
- **Minocycline** 50mg-100mg BID
- **Doxycycline** 50mg-100mg BID
- Alternatives:
- Erythromycin 250mg-500mg BID for children <8 years-old, Pregnancy
- Clindamycin
- Bactrim

## Bacterial Resistance

- Once thought rare in acne
- Now becoming a clinical problem
- Most common to erythromycin>clindamycin>tetracycline> doxycycline> minocycline

## Moderate Inflammatory Acne Treatment

**Hormonal Therapy**

- Oral contraceptives may be helpful in some women
- May take 3 months to see improvement.
- **Spiranolactone** useful in some.
- If acne is accompanied by irregular menses, female patterned hair loss or hirsutism, consider endocrine workup.

## Severe Nodulocystic, Scarring or Resistant Acne

**Isotretinoin**

- Synthetic oral retinoid
- 16-20 week course
- Regular laboratory evaluation and contraceptive counseling for females
- Registration with iPledge Program required



## Acne and Diet

- High Glycemic index diet causes hyperinsulinemia leading to increase in IGF-1
- Causes keratinocyte and sebocyte proliferation, lipogenesis
- Casacade of events activates androgens
- Observational studies suggest milk consumption imparts increased risk for acne

## Rosacea

- Papule and pustules
- Telangiectasias
- Flushing and blushing
- Sebaceous hyperplasia

- Triggers: cold, heat, UV, irritation, emotions, alcoholic beverages, spicy foods, hot beverages

## Rosacea Variants

- Opthalmic Rosacea- treatment of choice: oral antibiotics
- Steroid Rosacea- resulting from long term topical or systemic steroid use
- Perioral Dermatitis- triggered or aggravated by steroid use

## Rosacea Treatments

- Topical: clindamycin, erythromycin, metronidazole, sulfur-based lotions, azelaic acid, sunscreens, brimonidine, ivermectin
- Systemic: tetracyclines, erythromycin, isotretinoin

## Guttate psoriasis

- **scattered scaly papules**
- **trunk and proximal extremities**
- **can be associated with streptococcal infection**
- **can be seen as first sign of disease in children or acute exacerbation in adults**

## Nail Findings

- **nail pits**
- **yellowish discoloration beneath nail plate**

## Inverse psoriasis

- **commonly involves axilla, groin, umbilicus**
- **may not see much scaling**
- **higher risk of secondary infection**

## National Psoriasis Foundation Recommends:

- BP, pulse, BMI every 2 years
- Fasting blood glucose, lipid levels every 5 years if no additional risk factors, every 2 years with risk factors
- Joint status every visit- 5-8% of patients with psoriasis also suffer from PsA

## Psoriasis

- An immune dysregulatory disease secondary to T-cell activation, release of TH1 based cytokines. Cytokines cause keratinocytic proliferation and recruitment of inflammatory cells into the skin
- 2% of the U.S. population
- Bimodal incidence: peaks at ages 29 and 55
- Early onset associated with increased severity and family history

## Triggers

- Streptococcal infection (Guttate)
- HIV
- Drugs: Lithium, steroids, Beta-blockers, Interferons, ACE inhibitors, G-CSF

## Psoriasis Treatment-Topical

- Anthralin
- Vitamin D3 Analogues
- Tazarotene
- Tar
- Topical glucocorticoids

## Systemic Therapy

- PUVA
- Methotrexate
- Cyclosporine
- Retinoids- Acitretin
- Biologic Agents- Etanercept, Efaluzimab, Adalumimab, Alefacept, Infliximab, Secukinumab
- Apremilast

## Biologic Agents

- FDA Approved
  - TNF Inhibitors: Etanercept, Adalumimab, Infliximab
  - IL 17 Inhibitors: Secukinumab
  - P40 Inhibitors: Ustekinumab
- Investigational
  - Anti IL-17: Ixekizumab, Brodalumab

## Atopic Dermatitis

- Pruritus
- Facial/ Extensor involvement in pediatrics
- Flexural lichenification in adults
- Personal/ Family History of atopy

## Atopic Dermatitis- Associated Features

- Xerosis
- Cutaneous infections- *S. aureus*, Herpes, Molluscum
- Keratosis Pilaris
- Pityriasis Alba
- Nipple Eczema
- Elevated Serum IgE
- Orbital darkening

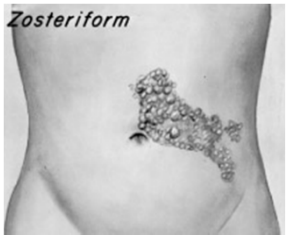
## Atopic Dermatitis and Food

- Prenatal and postnatal probiotic supplementation decreases risk
- Restriction diets helpful only if oral food challenge is positive

## Atopic Dermatitis- Management

- Emolients are key part of treatment
- Topical glucocorticoids
- Topical calcineurin inhibitors
- Antihistamines
- Phototherapy
- Systemic immunosuppression in severe disease
- On the horizon: Dupilumab acetyl dipeptide cream

## Zoster/ Shingles




•May involve multiple dermatomes or may be generalized in immunosuppressed patients

## Zoster/ Shingles

- **Varicella-zoster Virus**
- 2/3 of patients are over 50 years of age
- Risk factors: advanced age, malignancy, immunosuppression, xrt, HIV
- Reactivation of the virus in the sensory ganglia
- Consider if pt complains of pain in dermatomal distribution for more than 24-48 hrs even in the absence of skin lesions

## Zoster

- 5% with non-specific **prodromal** symptoms
- Preceded by **pain**, paresthesia in the involved **dermatome**
  - Pain may mimic acute abdomen or MI
- May involve multiple dermatomes or may be generalized in immunosuppressed patients

## Zoster

Diagnosis may be confirmed by:

- **Tzanck smear** –most rapid, non-specific
- Direct antigen detection – rapid, specific
- Viral culture

## Zoster- Therapy

**Treatment**

- Ideally initiate within 48-72 hours of rash
- Oral antiviral agents:
  - Acyclovir 800mg five times/day x 7-10 days
  - Valacyclovir 1gm TID x 7d
  - Famciclovir 500mg TID x 7d
  - IV Acyclovir for immunosuppressed patients

## Zoster- Pain Management

**Treatment of Acute Pain**:

- NSAID's
- Short course of Opiates
- +/- Systemic corticosteroids

Pain usually improves over weeks to months

**Treatment of Post-Herpetic Neuralgia**:

- Oral Tricyclics
- Capsaicin cream
- Topical Anesthetics
- Nerve blocks
- Gabapentin 1800mg-3600 mg/d
- Pregabalin 150-600 mg

## Zoster Prevention

- Decrease number of new cases of Zoster
- Decrease severity of Zoster outbreaks
- Decrease long-term consequences i.e. post-herpetic neuralgia
- Acceptable cost/benefit ratio

## Shingles Prevention Study

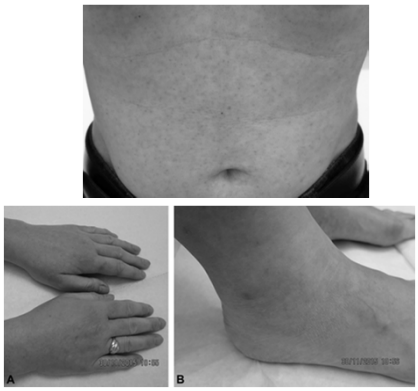
- Conclusions: Risk of Zoster reduced by 51% compared to placebo
- Effect greatest in 60-69 y/o
- FDA approved for people aged 50 years and older
- Reduced burden of illness by 61%
- Reduced incidence of PHN by 66.5%
- Reduced incidence of HZ by 51%

## Contraindications

- Any patient with a history of acquired or primary immunodeficiency states such as:
  - Leukemia/lymphoma
  - AIDS
  - High dose corticosteroids
  - Active unrelated tuberculosis
- Pregnancy
- Active Zoster
- History of anaphylactic reaction to gelatin, neomycin, or other vaccine component

## Zika Virus

- May 2015 confirmed in the Americas
- Arbovirus transmitted through mosquito bites, blood transfusions, sexual contact, mother to fetus
- Associations with microcephaly
- 3-12 day incubation
- Mild flu like symptoms, rash




*Journal of the American Academy of Dermatology* 2016 74, 1286-1287

## Zika Virus

- Diagnosis is made with reverse transcription pcr and ELISA the first 7 days
- Zika specific IgM Ab and plaque-reduction neutralization tests 4 or more days after onset

## Actinic Keratosis

- Common, pre-cursors to Squamous Cell Carcinoma- .025%-16%/yr progress to SCC
- Risk factors: age, male gender, fair skin, immunosuppression, lifetime sun exposure, albinism/ xeroderma pigmentosum
- UVB triggers genetic mutations in keratinocytes
- P53 most altered tumor suppressor gene in AK/ SCC
- Clinical: sun exposed areas, flat, erythematous, rough scale (better felt than seen)

## Actinic Keratosis- Therapy

- Cryotherapy
- Topical 5-Fluorouracil
- Imiquimod
- Diclofenac- NSAID
- Ingenol Mebutate
- Photodynamic therapy
- Dermabrasion/ chemical peels/ laser
- Systemic retinoids- transplant

## Basal Cell Carcinoma

- Most common cancer in the U.S.
- 80% of skin cancers
- Risk factors: male gender, fair complexion, UV, immunosuppression, family history, genetic syndromes, radiation therapy
- UV produces genetic mutations in p53 and PTCH genes
- Indolent growth pattern

## Basal Cell Carcinoma- Clinical Subtypes

- Nodular- translucent, pearly papule with telangiectasias
- Superficial- pink, scaly plaque with slight pearly border
- Morpheaform/ Sclerosing- skin-colored, pink or whitish, indurated plaque that resembles a scar

## Basal Cell Carcinoma- Therapy

- Excision- 4mm margin, 5-yr cure rate 89.9% (primary), 82.6% (recurrent)
- Curettage and electrodessication- 5 yr cure 92.3%
- Mohs surgery indicated for large, high-risk lesions (96-99%)
- Radiotherapy, 5-Fluorouracil, Imiquimod, Cryosurgery
- Vismodegib- Advanced/ Metastatic

## Vismodegib (Erivedge)

- Advanced basal cell carcinoma in poor surgical/ radiation candidates
- Hedgehog pathway inhibitor
- Metabolized by CYP
- 150mg daily
- GI, fatigue, weight loss, muscle spasms, arthralgias

## Sonidegib

- Hedgehog pathway inhibitor
- 200mg on empty stomach daily
- 58% reponse, lasted 2-19 mos
- Muscle spasms, headache, fatigue, GI, pain, itching
- Rare: rhabdomyolysis

## Squamous Cell Carcinoma

- Second most common skin cancer
- 20% of non-melanoma skin cancers
- Risk factors: male gender, age, life-time sun exposure, fair skin, chemical carcinogens, immunosuppression, chronic ulcers, burn scars, genetic syndromes, HPV, BRAF inhibitors
- Clinical : firm, skin-colored/ pink papules, plaques, head and neck of elderly
- May be associated with itching, pain, bleeding

## Squamous Cell Carcinoma

- Rate of metastasis approx 5%
- High risk
  - Large (>2cm), deep (>4mm), recurrent
  - Involvement of bone, muscle, nerve
  - Ears, lip, scalp, central face
  - Arising in scars, ulcers, burns, sinus tract, genitalia
  - Immunosuppressed
  - Arsenic exposure

## Squamous Cell Carcinoma

<u>Clinical Types</u>

- **SCC in situ (Bowen's Disease**)
  - Erythematous, scaly plaque
- **Nodular**
  - Erythematous, hyperkeratotic papule or nodule, exophytic or indurated
- **Oral**
  - White plaque or ulceration
  - Higher risk of metastasis

## Squamous Cell Carcinoma- Therapy

- Excision
- Mohs micrographic surgery- cure rate as high as 98.1% (<2cm), 74.8% (>2cm)
- Curettage and electrodessication
- Radiation- aggressive, recurrent, large, inoperable, poor surgical candidates
- Cryotherapy
- 10-yr survival with regional mets- 20%, distant- less than 10%

## Actinic Keratosis/ Squamous Cell Carcinoma

- SCC: Indurated erythematous lesions
- Treatment: surgical
- AK: pre-cursor to SCC
- UV radiation/ tanning bed use cause skin cancer
- P53 most altered tumor suppressor gene in AK/ SCC

## Melanoma

- Incidence rates increasing for 30 years
- Estimated 76,380 new cases anticipated this year
- Caucasians and men over 50 years are at highest risk
- Most common cancer ages 25-29 yo, second most common 15-29yo
- 10,130 expected deaths due to melanoma
- 5 year survival:
  - before spread 98%
  - regional spread 62%
  - Distant spread 16%

## Melanoma

- Fastest rising cancer, 1 person/hr will die of disease this year
- Steepest incidence rates: men>60yrs, lower Socioeconomic level
- Men have poorer survival
- Most common locations: back, chest, upper and lower extremities

## Melanoma

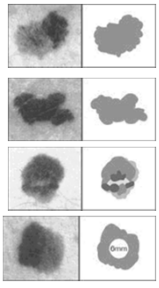
- May arise de novo or in a pre-existing mole (congenital nevus)
- Risk factors
  - Personal or Family History of melanoma
  - Fair skin
  - Sun exposure (esp childhood sunburns)/ Indoor tanning
  - Presence of dysplastic nevi
  - Childhood cancer, immunosuppression/ Parkinsons?

## Melanoma

- Lifetime Risk
  - 1 in 1500 born in early 1900s
  - 1 in 50 born in 2014
    - 1 in 200 for Hispanics, 1 in 1000 African Americans

## ABCD's of Melanoma

- **A-Asymmetry**
- **B-Border**
- **C-Color**
- **D-Diameter-6mm**
- **E-Elevation, enlargement**



## Melanoma

- Refer or biopsy if meets two of ABCD criteria or E
- Ugly Duckling Sign

## Melanoma

- Cumulative and prolonged exposure to UVB and/ or UVA
- Tanning bed use increases risk for melanoma by 75%

## Familial Melanoma

- Genetic basis (CDKN2A, CDK4, BRCA2, p53)
  - Primary family member with melanoma increases risk
  - >3 family members, consider medical genetic referral
  - 50% no mutation

## Melanoma- Clinical Subtypes

- Superficial Spreading Melanoma- 70%, ABCDE
- Acral Lentiginous Melanoma- predominant type in those of Asian, Latin, and African descent
- Nodular Melanoma- Sudden appearance and growth
- Lentigo Maligna Melanoma- $6^{th}$-$7^{th}$ decade of life, sun-exposed areas

## Superficial Spreading Melanoma

Most common type
Back: men
Legs: women

## Acral Lentiginous Melanoma

- More common in people with darker skin color/ African or Asian ancestory
- Diagnosis often delayed
- Check feet

## Nodular Melanoma

- Rapid growth
- Aggressive

## Lentigo Maligna Melanoma

- Chronically sun-damaged skin
- More common in elderly
- Slow progression

## Subungual Melanoma

- Most common on great toe or thumb
- Often history of trauma
- Refer to dermatology
  - >6mm width of dark streak
  - Asymmetric
  - Involves proximal nail fold
  - Nail dystrophy

## Amelanotic Melanoma

- May resemble psoriasis, dermatitis, basal cell, squamous cell carcinoma in situ
- Difficult diagnosis
- Clue: recent change or growth

## Melanoma

- Excisional Biopsy
- Key prognostic factors
  - **Thickness**
  - Ulceration
  - High mitotic rate
  - Lymph node involvement, distant metastasis

## Melanoma-Therapy

- Management
  - Lymph node evaluation for intermediate and thick lesions

## Melanoma- Management

- Excision: margins- 0.5cm- in situ, 1 cm <2mm, 2 cm $\geq$ 2mm
- Adjuvant therapy: interferon-alpha
- Palliative: radiation, chemotherapy, biologic therapy.
- Average survival of 6mos for Stage IV
- Novel therapy improves survival in some but key to management is early detection

## Stage IV Melanoma

- Ipilimumab (Intravenous)
  - CTLA-4 antibody
- Vemurafenib (Oral): target therapy for patient with BRAF mutation

  -improves survival, rapid response

  -BRAF mutation decreases with age
- Nivolumab (PD-1 antibody)
- Pembrolizumab (PD-1 antibody)

## Melanoma Web Based Learning

- INFORMED- Internet based program for early detection
  - www.skinsight.com/info/for_professionals/skin-cancer-detection-informed/skin-cancer-eduationc
- Assessing risk for melanoma
  - http://www.cancer.gov/melanomarisktool/

## Useful Resources

- INFORMED Skin Cancer Education
  - Priamary care doctors who review resources double likelihood of detection

## Skin Cancer Prevention

- SPF$\geq$ 30
- Broad Spectrum
- Water Resistant (40-80 minutes)
- 1 oz
- Protective clothing
- Shade (peak hours are 10am-4pm)

## Skin Cancer Prevention

- Use caution near water, snow, sand
- Get Vitamin D safely (diet and exercise)
- Avoid tanning beds

## Skin Cancer Prevention and Early Detection

- Educate patient about risks
- Teach patients about self skin exams
- Integrate skin exam into routine physical exams, esp. high risk patients

## Can Nicotinamide Prevent Skin Cancer?

- Nicotinamide 500mg bid x 12 mos
- 23% reduction in NMSC

NEJM Oct 2015

## Can ASA/NSAIDs Prevent Skin Cancer?

- Meta-analysis- 8 case-control and 5 cohort studies
- 50-400mg ASA was associated with reduced risk of NMSC

Oncol Lett. March 2015

## Can Coffee Prevent Skin Cancer?

- Coffee contains bioactive compounds
- Food questionnaire NIH-AARP study
- $\geq$ 4 cups/day was inversely associated with malignant melanoma

J Natl Cancer Inst Jan 2015

## Does Tea Count? And What About NMSC?

- Animal studies suggest caffeine helps prevent SCC
- Prospective study looking at risk of NMSC and Melanoma in relation to caffeine intake
- The amount of caffeine intake was inversely associated with BCC

Cancer Res Jul 2012

## Skin Cancer Prevention

- Annual skin exams
- Barriers: Time constraints, Competing comorbidities, Patient embarrassment
- Screening programs appear to be associated with decreased mortality
- Physician/ Health practitioner detected melanoma- thinner

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