DERMATOLOGY Potpourri

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Educational Things I HATE!!

- INDEX: Lupus, Systemic
  see *Systemic Lupus*
- Small Derm Photos
- Black and White Derm Photos
- Descriptive Photos/diagrams that don't label the point of interest
- Ambiguous Dogma

Things I'll Try My Best NOT To Do

- Small pictures
- Black and White
- Atypical Presentation Before Typical
- Tricks
- Play the 'clinical judgement' card

What is it?

Basic (?) Neuroscience….

"It's critical, of course, to note whether the Nikolsky sign is positive or negative…"

Hx

- A 23 y.o. grad student complains of rash for one week. Rash is 'all over', and mild-moderately pruritic
- SH/FH/ROS: nothing contributory
- No meds
- No known new contacts

Pityriasis Rosea: Definition

- pityriasis ion [Greek: *pitryon* bran + iasis]
  - "a name originally applied to a group of skin diseases characterized by the formation of fine branny scales, but now used only with a modifier"

Dorland's Illustrated Medical Dictionary 26th Edition
1981 WB Saunders (Philadelphia)

Pityriasis Rosea

- Common, benign, self-limiting, usually aSx
- Etiology? "there is some evidence that it is viral in origin" (Frat house and military base outbreaks)
- >75% between age 10-35 (mean = 25)
- Antecedent URI: 68.8%
- DDx: secondary syphilis, guttate psoriasis, viral exanthems, drug eruption

Habif T *Clinical Dermatology* 2004 Mosby (Philadelphia)

Pityriasis Rosea: Clinical

- Herald Patch: 2-10 cm round-oval lesion appears abruptly (17%)
  - Site: anyplace (trunk or proximal extremities most common)
  - May be mistaken for tinea
- Eruptive phase (mean 7-14 days post HP)
  - Max lesions within 2 weeks
  - Truncal mostly (6% extremity dominant)

Habif T *Clinical Dermatology* 2004 Mosby (Philadelphia)

Pityriasis Rosea: Clinical

- Lesions
  - Adults: oval plaques
  - Children, PG women, sometimes blacks: more commonly papular
- Lesion coloration
  - Caucasians: pink
  - Blacks: hyperpigmented
- Lesion orientation: skin lines ('Xmas tree')
- Fine wrinkled scale (collarette)

Habif T *Clinical Dermatology* 2004 Mosby (Philadelphia)

Rx: 2005

- Reassurance
- Antipruritics

Rx: 2006

"Use of high-dose acyclovir in pityriasis rosea"
Drago F, Vecchio F, Rebora A
Genoa, Italy

Pityriasis Rosea: Acyclovir

- PREMISE: HHV-6/HHV-7 associated?
- STUDY: consecutive PR patients (n=87) Department of Dermatology
- Rx: 7 d acyclovir 800mg 5 x/d vs placebo
- LAB (serology):
  - HHV-6, HHV-7
  - EBV, V-Z, CMV, Rubella, Parvo 19
  - Borrelia, Toxo

Drago F, Vecchio F, Rebora A "Use of high-dose acyclovir in pitryriasis rosea" J Am Acad Dermatol 2006;54-82

Pityriasis & Acyclovir: Demographics

	Acyclovir	Placebo
Age	28.4 (18-40)	26.5 (18-37)
Men	24	25
Women	18	20
Herald Patch	95%	84%
Systemic Sx	45.2%	35.6%
IgM HHV-6	2/24	2/19
IgM HHV-7	5/24	2/19

Drago F, Vecchio F, Rebora A "Use of high-dose acyclovir in pitryriasis rosea" J Am Acad Dermatol 2006;54-82

Pityriasis: Acyclovir Rx Success

Treatment	Partial Regression at Day		Complete Regression at Day	
	7	14	7	14
Placebo	22.2%	40%	4.5%	4.4%
Acyclovir	61.9%	11.9%	28.6%	78.6%

Drago F, Vecchio F, Rebora A "Use of high-dose acyclovir in pitryriasis rosea" J Am Acad Dermatol 2006;54-82

Pityriasis: Acyclovir Rx Success

Treatment	Onset of New Lesions at Day		Reduction of Systemic Sx at Day	
	7	14	7	14
Placebo	100%	55.6%	0%	2.2%
Acyclovir	40.5%	9.5%	36.8%	33.3%

Drago F, Vecchio F, Rebora A "Use of high-dose acyclovir in pitryriasis rosea" J Am Acad Dermatol 2006;54-82

Those Clever 1950's TV Ads

"__________ has been shown to be an effective decay-preventive dentifrice that can be of significant value when used as directed in a conscientiously applied program of oral hygiene and regular professional care."

Sodium lauryl sulfate and Recurrent Aphthous Ulcers

- PREMISE: 1989 study compared SLS-free TP with SLS-TP in allergic stomatitis patients
- STUDY: compare frequency of multiple minor recurrent aphthous ulcers in users of SLS TP vs SLS-free TP
- SUBJECTS: 10 healthy volunteers (lab screen WNL) with Hx multiple recurrent aphthous ulcers

Herlofson B, Barkvoll P. "Sodium lauryl sulfate and recurrent aphthous ulcers" Acta Odontol Scand 1994;52:257-259

Sodium Lauryl Sulfate and Recurrent Aphthous Ulcers

- METHOD: 3 month run-in with regular TP (all contained SLS) Rx : SLS-TP vs SLS-free TP X 3 months, then crossover
- RESULTS: mean ulcers = 17.8 → ↓ 5.1

Herlofson B, Barkvoll P. "Sodium lauryl sulfate and recurrent aphthous ulcers" Acta Odontol Scand 1994;52:257-259

Sodium lauryl sulfate and Recurrent Aphthous Ulcers

"The reasons for these results are not clear, but it appears likely that SLS may denature the mucosal mucin layers. Mucins are principal organic constituents of mucus, the visco-elastic material that covers all mucosal surfaces."

Herlofson B, Barkvoll P. "Sodium lauryl sulfate and recurrent aphthous ulcers" Acta Odontol Scand 1994;52:257-259

Some SLS-Free Toothpastes

- Biotene Dry Mouth Toothpaste
- CloSYSII Toothpaste
- Polar White Whitening Toothpaste
- Rembrandt Whitening Toothpaste
- Squiggle
- TheraBreath
- Tom's Maine Toothpaste

Accessed July 1, 2006 at www.dentist.net

Recurrent Apthous Ulcers

- Premise: incidental observation β-blocker (for another indication) → improvement in aphthous ulcer patients
- Study: (n=95) propranolol 30 mg/d X 7d, 20 mg/d X 7 d, 10 mg/d X 65d
- Inclusion: 2-7 ulcers at baseline, recurrences Q6-8 weeks
- Exclusion: herpes, Behcets

Goldman EK "β-Blocker Effective in Clearing Recurrent Aphthous Ulcers" Family Practice News 2002 (Nov 1):24

Recurrent Apthous Ulcers: Results

- Complete resolution: 72/95 (68%) v 6/84 (7.7%) placebo
- Partial improvement: 23/95 (32%)
- Some patients remain disease free X 3 years
- No adverse effects
- Subtherapeutic level of Rx for BP impact

Goldman EK "β-Blocker Effective in Clearing Recurrent Aphthous Ulcers" Family Practice News 2002 (Nov 1):24

Pseudofolliculitis Barbae (Razor Bumps)

- Ex: Curving hair growing back into skin
- 10-30 X more common in African Americans
- Standard Rxs:
  - D-C shaving
  - Dislodge hair with needle
  - Depilatories (Ba Sulfide, Ca Thioglycolate): 3-10 min application → ↓ hair shaft sulfide bonds → soft fluffy hair tip on breakage

Habif T P. Clinical Dermatology 3rd Edition 1996 Mosby (St Louis)

Eflornithine for Pseudofolliculitis

- STUDY: 10 AA men ≥ grade 3 Pseudofolliculitis, present at least 2 years
- Rx : eflornithine 13.9% cream (Vaniqa) b.i.d. X 16 weeks
- OUTCOME: PB severity scale ↓ ≥ 1 point 8/10 men

Tucker ME "Eflornithine Cream Helps Eliminate 'Razor Bumps in Black Men" Family Practice News 2001; October 15: page 9

Ptosis-related Stuff

- Which of the following is correct about apoptosis?
  - It is pronounced A-POP-TOE-SIS
  - It refers to the occurrence of programmed cell death upon injury
  - It is pronounced A-POE-TOSIS

The Apoptosis Story

"It is now indisputable that apoptosis plays an essential role in normal cell physiology and that aberrant apoptosis can manifest itself in a variety of human disorders."

Apoptosis: Biology and Mechanisms Kumar S, editor (Springer–Verlag Berlin) 1999

The Two Basic Kinds of Cell Death

APOPTOSIS	NECROSIS
Non-inflammatory involution	Inflammation
No tissue derangement	Tissue disorientation
No Scarring	Scarring
Functional Restoration	Functional Repair

Whence "apoptosis"….?

"The term apoptosis was suggested by Professor James Cormack of the Department of Greek, University of Aberdeen. It was used in classical Greek to describe the falling of leaves from trees. It seemed to encapsulate many of the ideas inherent in the apoptosis concept. Cormack advised us that the second 'p' should not be pronounced."

Kerr JFR "A Personal Account of Events Leading to the Definition of the Apoptosis Concept" Apoptosis: Biology and Mechanisms Kumar S, editor (Springer–Verlag Berlin) 1999

WHAT DOES PTOSIS STUFF HAVE TO DO WITH DERM?

AK
Actinic Keratosis

AK = SCC *in situ*

"Actinic keratosis is a squamous cell carcinoma confined to the epidermis."

Habif T. *Clinical Dermatology* 4th Edition 2004 Mosby (Edinburgh)

"Biologically, the AK is considered to be a carcinoma in situ."

Rigel DR Cancer of the Skin Elsevier (Philadelphia) 2005:53

"Solar keratoses are called 'precancerous' lesions; they are, in fact, cancerous already—early, superficial, and requiring time to manifest those characteristics of cancer. . ."

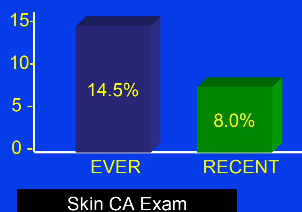
–R. L. Sutton, 1938

Sutton RL. *Arch Derm Syph.* 1938;37:737

Actinic Keratosis (AK): A Growing Problem

- Incidence and prevalence of AK and nonmelanoma skin cancers are increasing
- Key drivers:
  - Aging population
  - Increased outdoor activity
  - Migration to Sunbelt
  - Desire for cosmetic tanning
  - Immunosuppression – organ transplant

Skin Cancer Screening: Adults >18 BRFSS



Skin CA Exam

Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

What is the BRFSS?

- Annual nationwide telephone survey
- Conducted by state health departments with CDC assistance
- Adults (>18)
- Civilian
- Noninstitutionalized
- Self-report

Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

What Did BRFSS Look At? Prostate CA: Men > 50

- PSA testing within the past year for men without a DX of prostate CA
- DRE within the past year for men who have not been told they have prostate CA

Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

What Did BRFSS Look At? Breast and Cervical CA

- Women over age 40 who had a mammogram in the last year
- Women who had a Pap test within the preceding 3 years

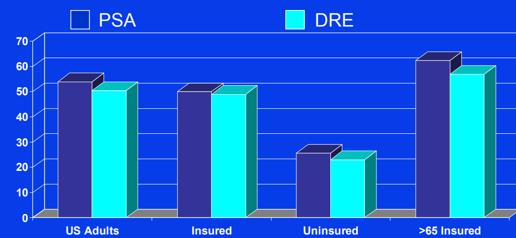
Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

What Did BRFSS Look At? Colon CA

- Flexible sigmoidoscopy or colonoscopy within the preceding 5 years
- FOBT home kit within the previous year

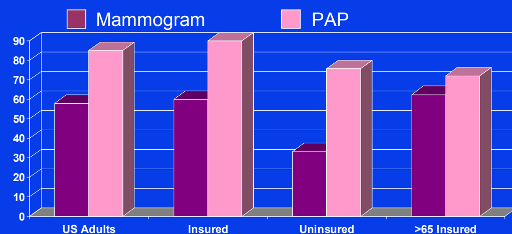
Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

BRFSS: Prostate CA



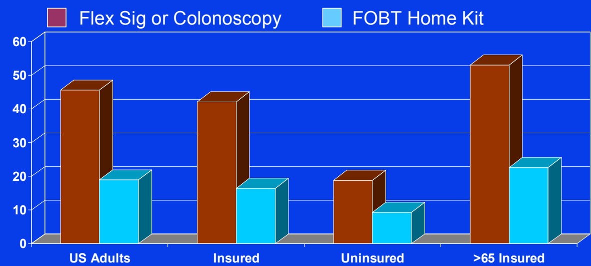
Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

BRFSS: Breast and Cervical CA



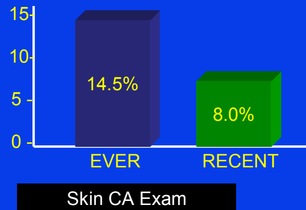
Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

BRFSS: Colon CA



Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

Skin Cancer Screening: Adults >18
National Center for Health Statistics 2000



Skin CA Exam

Smith RA, Cokkinides V, Harmon JE. "ACS Guidelines for the Early Detection of Cancer, 2006" CA Cancer J Clin 2006;56:11-25

EPIDEMIOLOGY

Epidemiology of Actinic Keratosis

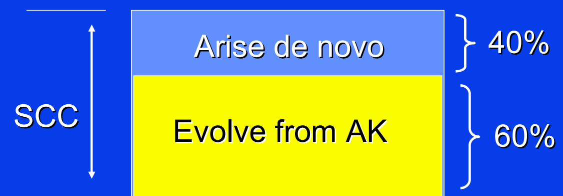
- Probably underdiagnosed
  - AK not reportable
  - Not included in cancer registries
  - Often treated without biopsy
- AK prevalence ↑ worldwide
- Regional variability
  - Clothing
  - Skin type
  - UVA/UVB intensity

PREVALENCE: WHAT SHOULD WE FOCUS ON?

SCC

Arise de novo } 40%

Evolve from AK } 60%



Stengel RM, Stone SP "Sun-Damaged Skin: Diagnosis and Treatment of Nonmelanoma Skin Cancer" Managing Common Skin Diseases (CME monograph) 2003;June:19-24

Disease Continuum of AK to Invasive SCC: Invasive SCC

Number of AKs	Relative patient risk for SCC
5 or fewer	1.0
6 - 20	4.0
> 20	20.0

Green A, et al. *Int J Cancer*. 1990;15:356-361.

What is the Risk of AK transformation?

"The risk that an individual lesion will become invasive has been estimated to be as high as 20%....."

Rigel DR Cancer of the Skin Elsevier (Philadelphia) 2005:53

What is the Risk of AK transformation?

"…. or may be as low as 0.1%"

Rigel DR Cancer of the Skin Elsevier (Philadelphia) 2005:53

AK Epidemiology: Australia

- Queenslanders continue to be overexposed to UV radiation
  - By age 3 years, 82% of people had been sunburned
  - Of these, one third had experienced a painful sunburn

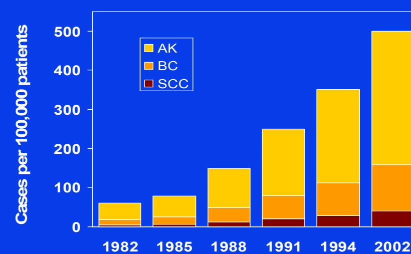
Stanton WR. *Aust NZ J Public Health*. 2000;24:178-184.

AK Epidemiology: Australia

- Survey of 1,040 Australians > age 40
  - Group A (59%): at least 1 visible AK
  - Group B (41%): free of visible lesions
- After 12 months of follow-up[1]
  - Group A: 60% developed new AK
  - Group B: 19% had developed AK

Marks R, et al. *Br J Dermatol*. 1986;115:649-655

AK Epidemiology: Europe



Stockfleth E 2005

SCC Incidence/100,000 Population

	MEN	WOMEN
Australia Nambour	600	298
Western Australia	775	501
Switzerland	29	18
US NH	97	32
US Arizona	271	112
Finland	7	4

Rigel DR Cancer of the Skin Elsevier (Philadelphia) 2005:53

Skin CA Consequences of Immunosuppression

"Skin cancer is the most common malignancy in the posttransplant setting and affects the majority of patients eventually."

Hampton T "Skin Cancer's Ranks Rise" JAMA 2005;294:12:1476-

AK: Relative Risk in Organ Transplant

	RR/100,000
AK	250
SCC	100
BCC	10
Kaposi's	500
Melanoma	5

Bouwes Bavinck JN et al. *Hum Exp Toxicol*. 1996.

Keratinocyte Carcinoma

"It is estimated that in 2004 there will be over 1 million cases of keratinocyte carcinoma (BCC/SCC) diagnosed in the US alone."

Rigel DR Cancer of the Skin Elsevier (Philadelphia) 2005:53

SCC in Persons < 40

- STUDY: Population-based retrospective incidence case review
- METHOD: Data analysis from healthcare sites in Rochester, MN (population 106,470)
- INCLUSION: persons < age 40 with BCC or SCC Dx 1976-2003
- PRIMARY OUTCOME: incident BCC and SCC and incidence change over time

Christenson LJ, Borrowman TA, Vacon CM, et al "Incidence of BCC and SCC in a Population Younger than 40 Years" JAMA 2005;294:681-690

SCC in Persons < 40: Results

- # Incident Cases SCC = 70
- Male = Female
- Average Incidence 3.9/100,000
- Incidence/100,000
  - 1976-1979 = 0.9
  - 2000-2003 = 4.1
- Incidence ↑ significantly (men and women)

Christenson LJ, Borrowman TA, Vacon CM, et al "Incidence of BCC and SCC in a Population Younger than 40 Years" JAMA 2005;294:681-690

Skin Cancer Mortality

While melanoma among whites is responsible for 90% of skin cancer deaths before 50 years of age, in adults over 85 years of age, the majority of skin cancer deaths are attributable to SCC."

Rigel DR Cancer of the Skin Elsevier (Philadelphia) 2005:53

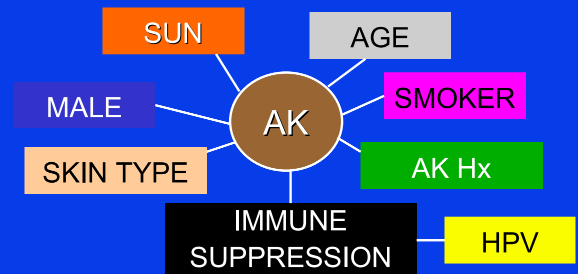
RISK FACTORS

Skin Cancer: Epidemiology

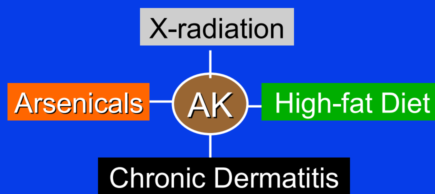
"The vast majority of all skin cancers are thought to be caused by exposure to UV radiation."

Rigel DR Cancer of the Skin Elsevier (Philadelphia) 2005:53

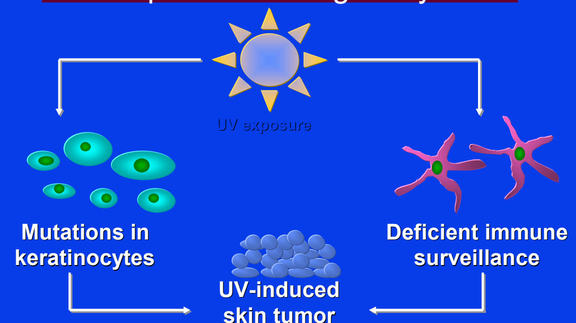
AK: Primary Risk Factors



AK: Secondary Risk Factors



Mechanisms of UV-Induced Epidermal Malignancy



AK Risk Factors: UV Exposure

- AK are present in sun-exposed areas
  - Head: face, neck, ears, scalp (hairless)
  - Anterior and upper chest
  - Forearms and dorsum of hand
  - Lips (actinic cheilitis)
- Outdoor occupations/recreational activities
- Tanning beds
- History of sunburn

Johnson TM, et al. *J Am Acad Dermatol.* 1992;26:467.
Ramani ML, et al. *J Am Acad Dermatol.* 1993;28:733.

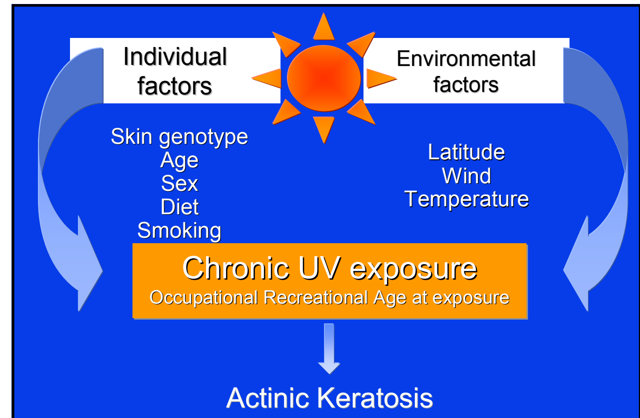
Actinic Keratosis Risk Factors: Skin Phenotype

- Baseline melanin = UV protective
- Susceptibility of white skin
  - inability to tan
  - predisposition to sunburn
- Fair skin: Fitzpatrick I to III
- Blue eyes
- Blond or red hair

Frost CA, et al. *Br J Dermatol.* 1994;131:455

NMSC in Chronic Immunosuppression

- Occur an average of 30 years earlier
- More frequently multiple
- Increased rate of recurrence
- Increased rate of metastasis
- May have more rapid rate of growth
- May resemble warts or keratoacanthomas



Ultraviolet Radiation

- UV radiation begins and sustains the process
- Chronic sun exposure damage is cumulative
- UVB: primary carcinogen
- UVA is synergistic

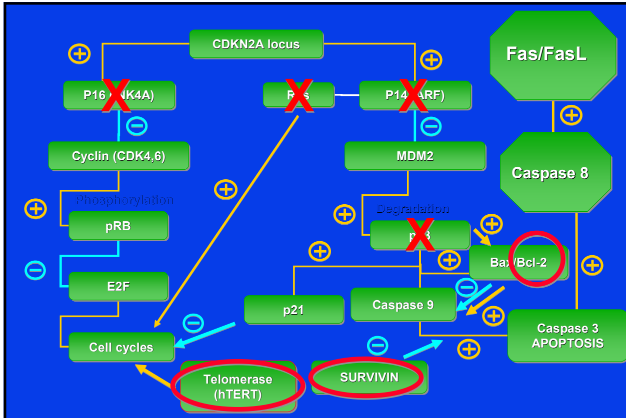
Diagnosis

Photocarcinogenesis: Changes in Gene Expression

- ↑ expression of genes associated with proliferation and cell survival
- ↓ expression of genes associated with apoptosis
- Progressive down-regulation of genes necessary for T cells to respond to tumor antigens

p53 Tumor Suppressor Gene: Initiation

- DNA repair genes are also UVR targets
- Continued XS UVR may → ↓ DNA repair
- → mutations of the *p53* gene itself
- Additional genetic mutations accumulate
- Cells become ↑ resistant to apoptosis
- Affected mutated cells have growth advantage
- → subclinical clonal expansion (initially) → clinical AK → invasive SCC



Photocarcinogenesis: Changes in Gene Expression

- ↑ expression of genes associated with proliferation and cell survival
- ↓ expression of genes associated with terminal differentiation and apoptosis
- Progressive down-regulation of genes needed for T cells to respond to tumor antigens

Actinic Keratosis

- No one can predict which lesion is going to evolve to invasive SCC so:

Wouldn't It make the most sense to treat ALL ACTINIC KERATOSES?

Treatment of AK: Aim

- Prevention of SCC invasion and metastasis
- Relief of symptoms
- Improvement of cosmetic appearance
- Reduce likelihood of new lesions
- Proactively treat subclinical lesions

Treatment of AK: Considerations

- Number of lesions
- Size
- Location
- Ability of patient to comply
- Patient preference characteristics
- Success with previous therapies
- Cost of treatment

Treatment of AK: Lesion-Directed Rationale

- Minimizes unnecessary treatment of surrounding "healthy skin"
- May prevent the development of invasive SCC
- Ideally should not induce dyschromia
  - Hypopigmention will accelerate the further accumulation of UV damage

Treatment of AK: Lesion-Directed Options

Treatment	MOA
Cryotherapy	Freeze cells
Curettage and electrodescication	Mechanical scraping
Excision	Excision
Laser	Burn cells

Lesion-Directed: Cryotherapy

- Most common treatment
- Single freeze-thaw times of < 5 seconds result in CR rates of only 39%
- Hypopigmentation is present in 29% of completely responding lesions
- Hyperpigmentation found in 6% of Rx lesions
- Cryotherapy can cause significant pain

Thai KE, et al. *Int J Dermatol.* 2004;43:687-692.

Treatment of AK: Topical Field-Directed Options

Treatment	MOA
Imiquimod	Immune response modifier
5-Fluorouracil	Antimetabolite
Chemical peels	Destruction
PDT-ALA/MAL	Free radical production
Diclofenac	NSAID

Diclofenac Sodium Gel

- Inhibits arachidonic acid → prostaglandin conversion
- Indicated for AK only
- 3% gel, applied twice daily for 12 weeks
- Complete AK clearance = 30–50% patients
- Adverse Events (AEs): pruritus, application-site reactions, contact sensitization

Jorizzo JL. *J Cutan Med Surg.* 2005;8(suppl 3):13–21.
SOLARAZE® GEL (diclofenac sodium 3%) 2005 PI

Actinic Keratosis: Lifestyle Changes

- Inform about SCC/AK relationship
- Regular use sunscreen (SPF 30)
- Minimize excessive sun exposure
- Avoid: tanning parlors, sunbathing, sunburn
- Use of hats and protective clothing

Summary

- An AK lesion is the "tip of the iceberg"
  - Management should be directed toward the disease process
  - Field-directed therapy allows for the treatment of subclinical lesions
  - Long-term follow-up is necessary because risk of disease progression
- AKs: a "wake-up" call

Acne

In the community primary care setting, which regimen is most cost effective Rx for acne?

- PO tetracycline
- PO minocycline
- Topical benzoyl peroxide
- Topical benzoyl peroxide + erythromycin combined
- Topical erythromycin (AM) + Benzoyl peroxide (PM)

A RCT of Acne Rx in the Community

PREMISES

- Acne point prevalence ± 100% in adolescents
- *P acnes* resistance ↑ since 1990's, hence old data may not reflect current resistance
- Few studies compare efficacy and cost effectiveness in community setting

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community

DESIGN

- Industry-independent
- Community-based, observer-masked, randomised trial
- Pts recruited from GP offices and local colleges

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community

INCLUSION

- Mild-moderate acne (grade ≤ 3)
- ≥15 inflamed and 15 non-inflamed facial lesions at baseline
- Able to stop existing acne Rx (if any) ≥ 4 weeks prior to study initiation

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community

EXCLUSION

- Primarily truncal, nodular, or secondary acne
- Pregnancy/breast feeding
- Onset > age 26
- Comorbid facial dermatopathology
- Significant systemic disease
- Previous Rx with isotretinoin
- Current Rx by dermatologist
- Medications interacting with study drugs

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community

Rx Regimens

1) Oxytetracycline 500 b.i.d. PO + placebo cream b.i.d.
2) Minocycline 100 mg SR PO QD + placebo cream b.i.d.
3) Benzoyl peroxide 5% b.i.d. + Placebo PO QD
4) Benz peroxide 5%/Emycin 3% b.i.d + Placebo PO QD
5) Erythromycin 3% QAM, Benzoyl peroxide 5% QPM

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community

Outcomes (6, 12, and 18 weeks)

- % with ≥ moderate improvement (6 point scale)
  - Mirror and baseline photograph used for assistance
- # of inflamed facial lesions
- ‘Willingness to Pay’
  - How much would you pay for this Rx compared to a Rx that could completely clear your acne?
- QOL, AEs
- Baseline *P acnes* resistance pattern impact

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community

≥ Moderate Improvement	#1 (Tet)	#2 (Min)	#3 (BP)	#4 (BP+E)	#5 (BP ¦¦ E)
As per participant	55%	54%	60%	66%*	63%
As per assessor	50%	51%	57%	59%	60%
↓Number inflamed lesions	27.8	29.9	22.3	24.5	26.9

* P <0.05 compared to regimen #2

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community: Impact of *P acnes* colonization

- e-mycin resistant colonization → no impact upon proportion with at least moderate improvement using e-mycin based regimens
- Tetracycline resistant colonization → impact upon tetracycline regimens (↓moderately improved rate > 50%)

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community: Conclusions

- “Differences in efficacy were small and generally not statistically significant. In particular, modified-release minocycline, the most expensive regimen, was not found to be superior, a finding that concurs with a recent Cochrane systematic review”

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

A RCT of Acne Rx in the Community: Conclusions

“Benzoyl peroxide alone was the most cost-effective regimen….it represents the best value antimicrobial for first-line use.”

Ozolins M, Eady EA, Avery AJ, et al Lancet 2004;364:2188-2195

Acne & Antibiotics: What’s the ‘Right Dose’?

- You have decided to Rx acne in this 19 y.o. male patient with doxycycline. What is the ‘right’ dose?
  - doxycycline 100 mg b.i.d.
  - doxycycline 500 mg b.i.d.
  - doxycyline 20 mg b.i.d.

Subantimicrobial-Dose Doxycycline

- Study: DBRPCT (n=51) adults with acne
- Rx: doxycycline hyclate 20 mg b.i.d. (Periostat) vs placebo x 6 months

Outcomes:

- *Primary*: Δ from baseline # inflammatory, noninflammatory, and total acne lesions
- *Secondary*:
  - Δ from baseline # papules, pustules, nodules
  - Physician and Pt global assessment

Skidmore R "Effects of Subantimicrobial-Dose Doxycycline in the treatment of Moderate Acne" Arch Derm 2003;139:459-464

Subantimicrobial-Dose Doxycycline Conclusions

"Twice-daily subantimicrobial-dose doxycycline treatment significantly ↓ the # of inflammatory and noninflammatory lesions in patients with moderate facial acne, was well tolerated, had no detectable antimicrobial effect on the skin flora, and did not result in any increase in the number or severity of resistant organisms."

Skidmore R "Effects of Subantimicrobial-Dose Doxycycline in the treatment of Moderate Acne" Arch Derm 2003;139:459-464

Subantimicrobial-Dose Doxycycline

Results (all $p < 0.05$ favor Rx)

- % reduction # comedones, inflammatory and noninflammatory lesions
- Total inflammatory lesions
- Clinician's global assessment
- No change in bacetrial count

Skidmore R "Effects of Subantimicrobial-Dose Doxycycline in the treatment of Moderate Acne" Arch Derm 2003;139:459-464

'Secondary' Acne

A 24 year old woman with moderate-severe cystic acne over her face, chest, and back says that she has had persistent acne since adolescence, and that 'regular acne medicines' don't work. What pathologic defect might be causing her acne?

- Adrenal Enzyme Defect
- Dermatitis Artifacta (self induced dermatitis)
- Progestasert IUD
- Zinc deficiency

Educationally Resistant California FP Learns Lesson: September 1976

J.D. 24 y.o. Caucasian 🕮 severe cystic acne

- CC: "My doctor in Massachusetts says I have too much male hormone and need steroids"
- HPI: Acne since age 15, on dexamethasone since age 19 . Menses regular; no hirsutism
- PE : florid facial acne scars, some active lesions. Acne on upper back and chest Otherwise WNL

Educationally Resistant California FP Learns Lesson: T^0 = September 1976

- Assessment: Acne
- Plan:
  - dexamethasone not indicated
  - Benzoyl Peroxide + Tetracycline
- JD: "That stuff just doesn't work"
- Plan: "OK, we'll use Xtra strength…."

Visit #2 JD T^0 + 4 weeks

- CC: No Δ
- PE: No Δ
- Assessment: It just hasn't been enough time
- PLAN: trial 4 more weeks same
- JD: "I'm telling you, this stuff won't work; but OK, I'll keep tryin"

Visit #3 JD T^0 + 8 weeks

- CC: No Δ
- PE : Same
- PLAN: Curbside local derm guy

Visit #3 JD

- ME: "Hey Don, got a lady here with blah blah blah blah. She said something about needing steroids. I gave her blah blah blah, what do you think should be next?"
- DON the local derm guy: "I don't see any reason why she needs steroids. Since she's used tetracycline before, maybe try some erythromycin instead, Lou."

Visit #4 JD T^0 + 12 weeks

- CC : No Δ on erythromycin
- PE : same
- PLAN: Repeat curbside

Visit #4 JD: Repeat Curbside

- ME: " Hey Don, do you remember that pt I called you about last month who says her dermatologist gives her dexamethasone for an androgen XS"
- DON: "Sure. What's up?"
- ME: "Well, she's still no better with the switch to erythromycin."

Visit #4 JD: Repeat Curbside

- DON: "Is she hirsute? Periods messed up?"
- ME: " Nope"
- DON: "What keratolytic have you tried?
- ME: "Just benzoyl peroxide so far."
- DON: "Give her a 4-8 week trial of a sulfur-based keratolytic"
- PLAN A (ME): sulfur keratolytic
- PLAN B (JD): call Massachusetts

Visit #5 JD T^0 + 16 weeks

- CC "Will you read this article? My dermatologist, who wrote it, sent it for you."

Adrenocortical Hydroxylase Deficiencies in Acne Vulgaris: 11 female acne patients with inadequate response to standard treatment

Rose L J Invest Derm 1976;66(5):324-326

Introduction: Reports have appeared of a favorable response to low dose glucocorticoids in women with acne who have failed traditional treatments. Some patients may have partial adrenocortical hydroxylase deficiencies with attendant elevated androgen levels"

Hmmmm.............well...... I better read some more of this...........

Adrenocortical Hydroxylase Deficiencies in Acne Vulgaris: 11 female acne patients with inadequate response to standard treatment
Rose L J Invest Derm 1976;66(5):324-326

- ACTH stimulation → ↑ adrenal androgens consistent with partial 11-hydroxylase or 21-hydroxylase deficiency (7/11 pts)
- 11-OH → ↑ DHEA-S
- 21-OH → ↑ 17OH-PG
- Responds well to dexamethasone

Visit #6 (Phone) JD T^0 + 16 weeks + 1 day

- So where can I call in that dexamethasone for you….?

University of Florida Department of Family Medicine Noon Conference December 1989

- TOPIC: Management of Acne
- SPEAKER: Academic Dermatologist, University of Florida (Jacksonville)
- QUESTION from the audience: "What is the role of androgens in acne?"
- RESPONSE: "It is not worth evaluating"

Sent to Clinician Noon Conference Attendees December 1989

Correcting Endocrinopathy is Cited as Key to Treating Acne

" In spite of the well-known fact that sebum production is related to the amount of androgen, this has aspect has been disregarded in many of the patients whose acne has been unsuccessfully managed with conventional therapies"

Samuel P Marynick, Baylor College of Medicine, 63rd Annual Meeting of the Endocrine Society of America

Sent to Clinician Noon Conference Attendees December 1989 : Case Study and f/u

Lowering Androgens Often Resolves Severe Acne

- Case: 25 y.o. ♂ resistant acne X 10 years
- Rx: Consulted and Rx by 18 dermatologists
- Lab:
  - 17-OH Prog > 4X ULN
  - DHEAs > 3X ULN
- Dx: Partial adrenocortical enzyme deficiencies
- Followup: Generated subsequent study

Medical World News 1981(September 1):25

Sent to Clinician Noon Conference Attendees December 1989 : Case Study and f/u

Lowering Androgens Often Resolves Severe Acne

- STUDY:100 consecutive severe acne pts deemed 'unresponsive' (=failed antibiotics benzoyl peroxide, topical retinoic acid)
- LAB : DHEAs, 17-OH Prog, Testosterone

Medical World News 1981(September 1):25

Sent to Clinician Noon Conference Attendees December 1989 : Case Study and f/u

Lowering Androgens Often Resolves Severe Acne

- RESULTS: androgen ↑most patients
- Rx: Dexamethasone 0.25 mg/d (up to 0.5 mg if DHEA remained elevated)
- Results (All ♀,most ♂) : acne improved

Medical World News 1981(September 1):25

Sent to Clinician Noon Conference Attendees December 1989 : 'Medical News' JAMA

Suspect endocrine disorder in cases of severe adult acne

- STUDY: 139 📖 referred to UT Houston Dept of Reproductive Medicine after chronic acne Rx (1-15 yrs)
- Androgen ↑most patients
  - testosterone > 50th percentile = 90%
  - regular menses = 39%

Medical News' JAMA 1981;246(13):1391

Androgen : Ovarian Neoplasm

- "The most important reason to evaluate patients with androgen excess is to rule out neoplasms of the ovary or adrenal, although these will be extremely rare."
  - Serum TsT > 2.5 X WNL → US pelvis
  - If US WNL → CT Abd (? adrenal mass)

Lobo R Ob & Gyn Clin of N America 1987;14(4):955-967

Androgen XS : Cystic Acne

- Study 132 📖 54 🔔 severe cystic acne (unresponsive > 1yr)
- Measured: DHEA-S, 17-OH Prog, TsT
- Rx: (📖) Dexamethasone begin 0.125 mg/d ↑ Q30d up to 0.5 mg/d OR DHEA-S ≤ 2.0 mcg/ml
- (🔔) Dexamethasone begin 0.25 mg ↑ Q30d up to 0.75 mg OR DHEA-S ≤ 3.0 mcg/ml
- Outcome: acne improvement directly correlated with changes in DHEAs

Marynick S NEJM 1983;308(17):981-986

Androgen XS : Cystic Acne

🕮 🔔

age	24.7 (17-42)	21.5 (15-36)
duration (years)	8.1 (1-29)	7.2 (2-24)
DHEA-S > WNL	80%	81%
17-OH Pg > WNL	14%	34%
TsT > WNL	17%	

Overall outcome: Acne improvement ≈ ↓ DHEA-S

Marynick S NEJM 1983;308(17):981-986

Androgen XS : Rx Options

- 35 💻g estrogen/d →↑ SHBG →↓ unbound androgen (standard OC ethinyl estradiol)
- Use least androgenic progestin (gestodene, norgestimate, desogestrel generation OC's)
- QHS dexamethasone 0.2-0.5mg/d suppresses androgen; goal : DHEA-S < 1💻g/ml
- Spironolactone 50-200mg/d ; ↑K+ not seen in healthy population

Lobo R Ob & Gyn Clin of N America 1987;14(4):955-967

Androgen XS : Rx Options

- Cyproterone: progestin/antiandrogen taken up and released slowly by fat.
- Germany : 96% acne pts Rx with combination OC ethinyl estradiol 50💻g + cyproterone acetate 2 mg (Diane™) improved

Lobo R Ob & Gyn Clin of N America 1987;14(4):955-967

XS Androgen : When to Screen

Acne hormonal evaluation indicated in :

- every 🕮 with hirsutism
- very early onset acne
- very late onset acne
- resistant to standard treatments
- relapse after isotretinoin (Accutane)

Shelley W. Cutis 1993;52(Nov):257-264

"Androgen Source Key to Dx in Acne with Hirsutism"

- acne without hirsutism may be sign late onset adrenal hyperplasia (🔔 = 🕮)
- Low dose prednisone is effective Rx
- "Congenital adrenal hyperplasia is common in this country, with an incidence of 1%"

Bates W Family Practice News May 15, 1994

Hormonal Rx of Acne:

Shalita AR Current Therapy 2003;841-843

- "Inflammatory acne in women may be the result of ↑androgens, either of adrenal or ovarian origin"
- "OCs…not only suppress ovarian androgen but also DHEA from the adrenal"
- OCs may be used to Rx acne in women without any other evidence of an androgen disorder"
- Similarly, patients with elevated DHEAs can be Rx with low-dose prednisone or dexamethasone"
- "…with hirsutism, spironolactone is frequently beneficial in combination with OCs"

Hormonal Treatment of Acne: Indications

OCs	Spironolactone	Oral Steroids
Fail antibiotics	Fail antibiotics	↑ DHEAs
Fail steroids		Fail antibiotics
↑ testosterone		Fail isotretinoin
		Fail OCs
		Fail spironolactone

Habif T Clinical Dermatology 2004 (Mosby, Philadelphia)

Androgen Source: adrenal? ovarian?

- Normal TsT = 30-60 ng/ml (60% adrenal, 40% ovarian)
  - normal adrenals contribute 18-36 ng/ml
  - normal ovaries contribute 12-24 ng/ml
- Dexamethasone suppression can maximally reduce TsT 36ng/ml (60% X 60 ng/ml); anything greater represents adrenal overproduction

Androgen Source: adrenal? ovarian?

Example 1

- M.S. evaluation for refractory acne
  - total TsT = 90 ng/ml
  - post-dexamethasone TsT = 30 ng/ml
  - adrenal production = 60 ng
- Dx : adrenal overproduction
- Rx: low dose dexamethasone

Ovarian? Adrenal? Example 2

- 24 y.o refractory acne
  - TsT = 100 ng/ml
  - postdexamethasone TsT = 80 ng/ml
- ∴ adrenals contrib 20 ng/ml, ovaries 80 ng/ml
- normal ovarian contribution is ≤ 24 ng/ml
- Dx: Ovarian overproduction Rx: OC' s
- Is this ovarian neoplasm?
- Not likely at TsT < 200ng/ml (Rarely 150-200ng/ml)

Adrenal? Ovarian? Example 3

- 24 y.o TsT = 100 ng/ml
- post dexamethasone TsT = 50 ng/ml
  - adrenal contribution = 50 ng/ml (max = 36ng/ml)
  - ovarian contribution = 50 ng/ml (max = 24 ng/ml)
- Dx: Adrenal & Ovarian Excess production
- Rx: dexamethasone suppression + possibly OC's depending upon patient's response

Ovarian? Adrenal? Example 4

- 25 y.o TsT = 58 ng/ml
- Because of hirsutism & menstrual irregularities, decided to try dexamethasone suppression
- Post suppression TsT = 12 ng/ml
- adrenal contribution = 46 ng/ml (max = 36)
- ovarian contribution = 12 ng/ml (= WNL)
- Dx: adrenal overproduction Rx: dexamethasone

Spironolactone Mechanisms

- Antiandrogen:
- Direct androgen receptor antagonist
- ↓ovarian TsT production
- ↓ ovarian and adrenal androstenedione
- ↑TsT clearance
- Effects dose- related (most hirsute pts require ± 200 mg/d)

Lobo R Ob & Gyn Clin of N America 1987;14(4):955-967

Spironolactone for resistant acne

- 8 patients, failed 6 months erythromycin + 5% benzoyl peroxide
- Rx : 200 mg spironolactone QD X 3 months
- 6/8 patients → significant improvement (mean overall ↓ 52%)
- Sebum excretion rate ↓maximally by 30 days and maintained

Burke B Br J Derm 1984:124-125

Spironolactone for resistant acne

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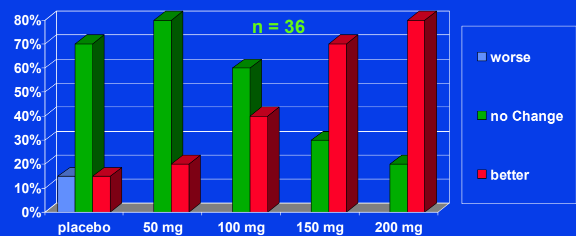
Burke BM Br J Derm 1984:124-125

Spironolactone for Acne



consecutive & pts referred for severe acne

Goodfellow A Br J Derm 1984;111: 209-214.