NORTH CAROLINA DERMATOLOGY ASSOCIATION

2016 Summer Meeting

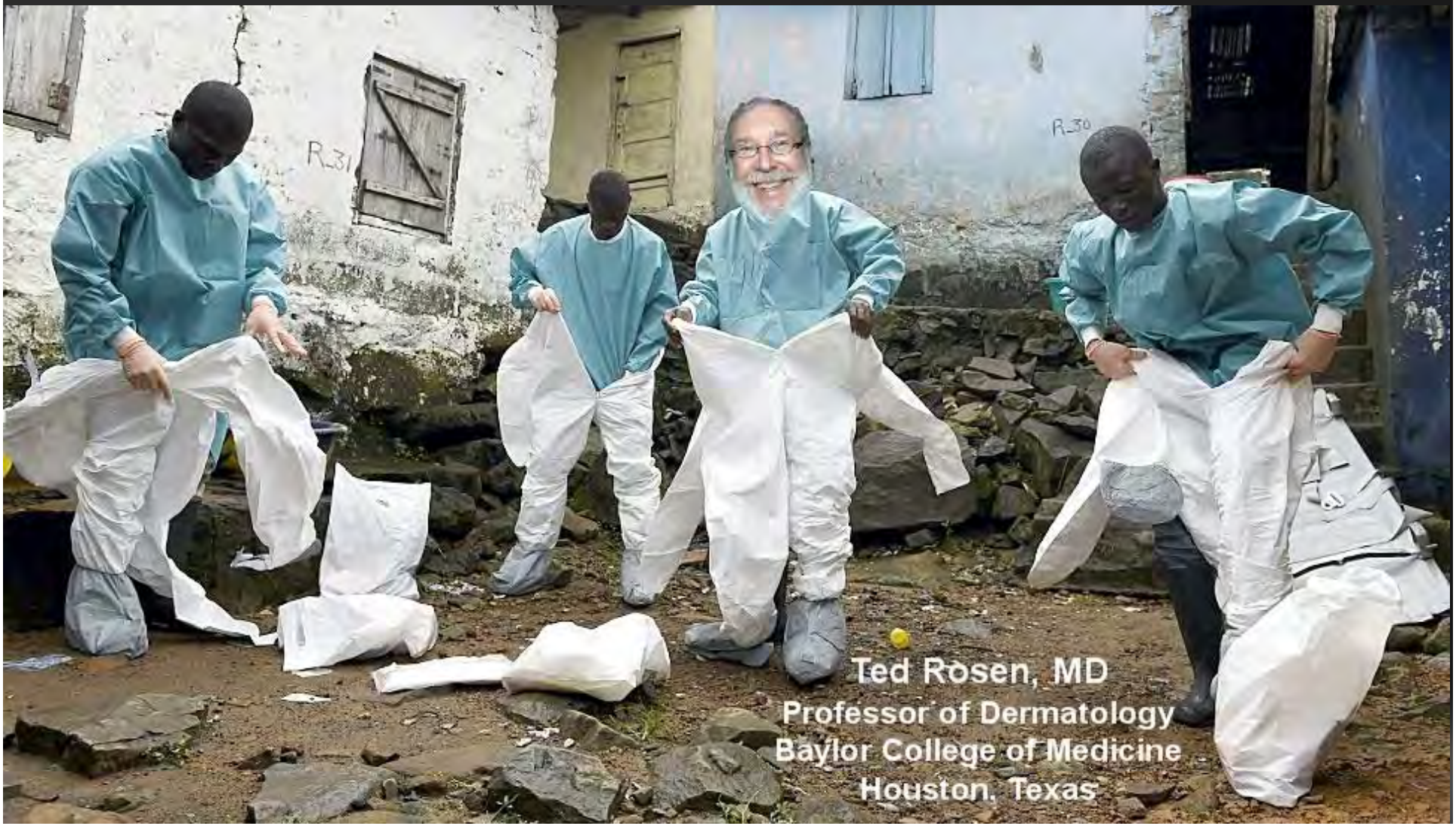
PRESENTATION SLIDES FOR FRIDAY, JULY 8


Where the hell is Sierra Leone, and WHAT does this guy have?
EBOLA?
Infectious Diseases Therapy: 2015

Ted Rosen, MD
Professor of Dermatology
Baylor College of Medicine
Houston, Texas

Infectious Disease Therapy: 2016

Your Host (No pun intended)



Conflict of Interest Disclosures

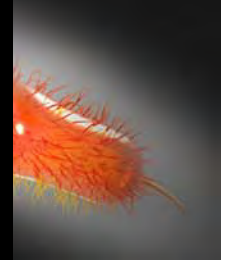
- **I have received honoraria for attending or moderating advisory board meetings for the following proprietary entities producing health care goods or services discussed in or related to the content of this CME talk: Anacor, Cipher, Valeant**
- **The content of this talk will reference commercial products; however, I will use generic terms whenever possible and alternative therapies will be discussed**
- **I will discuss unapproved or investigative use of commercial products or devices, of necessity, due to the nature of this presentation; I will disclose when an unapproved or an investigational product or device is under discussion**

Every day, worldwide…..

100,000,000 Copulations

910,000 Conceptions

350,000 New cases of STD



HIV: Still a Problem

GLOBAL

- Living with HIV 37 x 10^6
- Incidence: 2 x 10^6
- Cumulative AIDS mortality 36 x 10^6
- Once tested & diagnosed 43% engage in care

USA

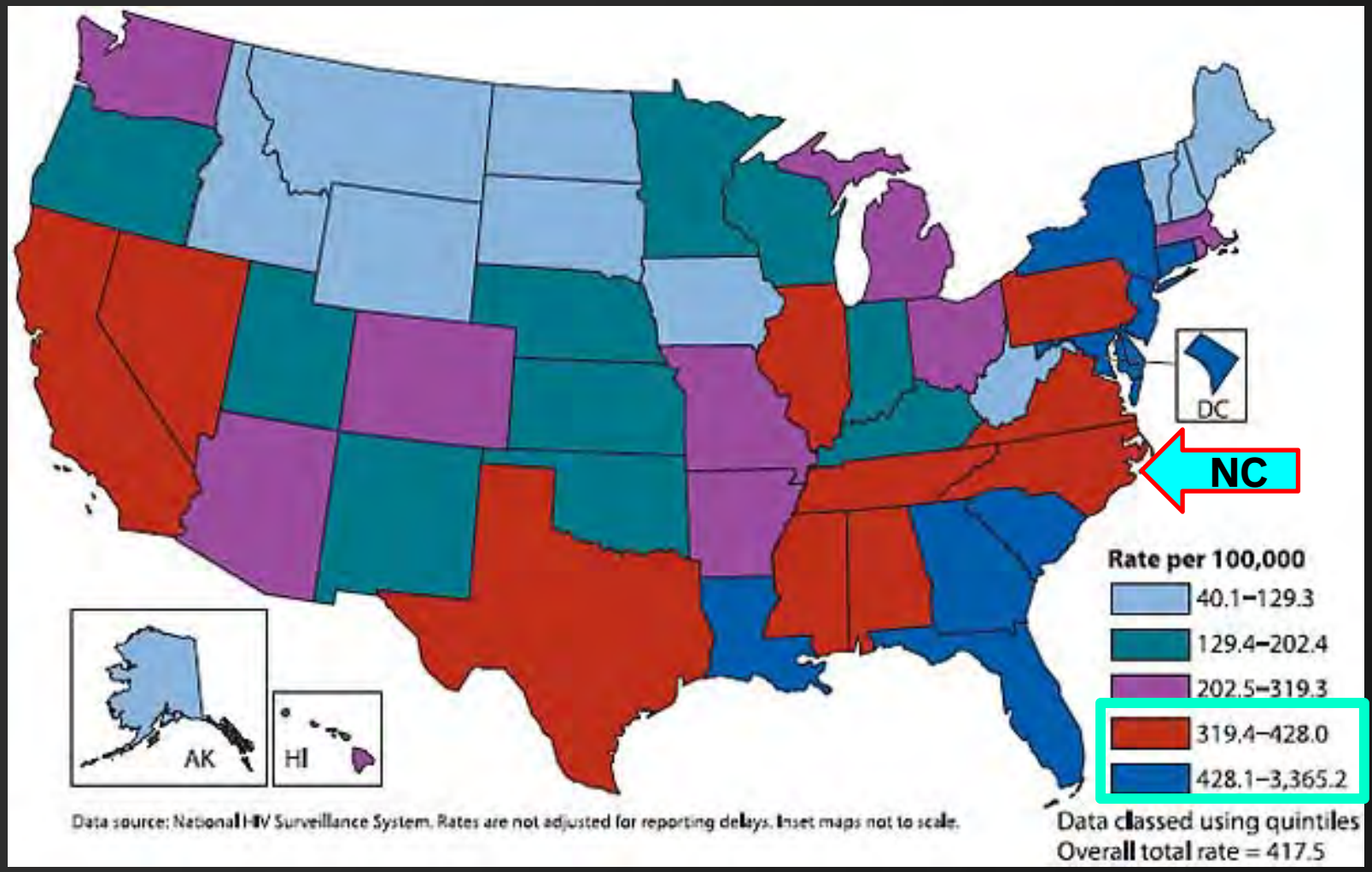
- Living with HIV 1.2 x 10^6
- Incidence 50,000
- Cumulative AIDS mortality 658,000
- Once tested & diagnosed 40% engage in care

http://www.cdc.gov/hiv/statistics/overview/ataglance.html

EVERY 9.5 MINUTES

SOMEONE IN THE U.S. IS INFECTED WITH HIV

CDC. HIV Surveillance Supplemental Report 2013;18(No. 5).
Published October 2013.



http://www.cdc.gov/hiv/statistics/overview/geographicdistribution.html

Antiretroviral Drugs 2016

Reverse Transcriptase Inhibitors

Nucleoside analogues
- zidovudine (AZT,ZDV)
- didanosine (ddI)
- zalcitabine (ddC)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)

Nucleotide analogue
- tenofovir (TFV)

Non-nucleoside analogues
- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETV)
- rilpivirine (RPV)

WHEN TO TREAT?

Protease Inhibitors

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- amprenavir (APV)
- lopinavir/r (LPV/r)
- fosamprenavir (FPV)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)
- dolutegravir (DTG)

Integrase Inhibitor (2)

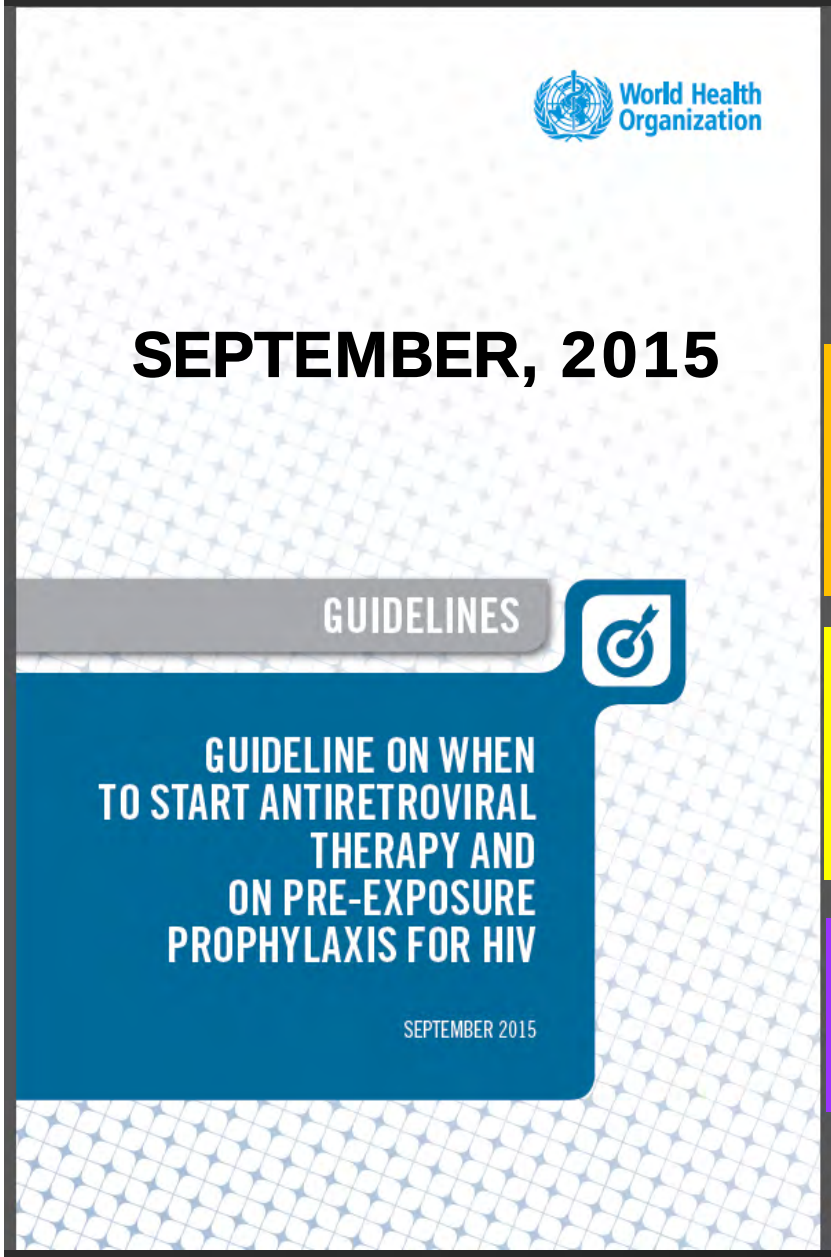
- raltegravir (RAL)
- elvitegravir (ELV)

Fusion Inhibitor

- fuzeon (T20)

Entry Inhibitor (CCR5)

- maraviroc (MVC)



cART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count

cART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong

cART should be initiated among all infants, children and adolescents living with HIV regardless of WHO clinical stage and at any CD4 cell count

Estimate: expanding cART to all HIV+ people will avert 21 million AIDS-related deaths & 28 million new infections by 2030

http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

Jean-Michel Molina, M.D., Catherine Capitant, M.D., Bruno Spire, M.D., Ph.D., Gilles Pialoux, M.D., Laurent Cotte, M.D., Isabelle Charreau, M.D., Cecile Tremblay, M.D., Jean-Marie Le Gall, Ph.D., Eric Cua, M.D., Armelle Pasquet, M.D., François Raffi, M.D., Claire Pintado, M.D., Christian Chidiac, M.D., Julie Chas, M.D., Pierre Charbonneau, M.D., Constance Delaugerre, Pharm.D., Ph.D., Marie Suzan-Monti, Ph.D., Benedicte Loze, B.S., Julien Fonsart, Pharm.D., Gilles Peytavin, Pharm.D., Antoine Cheret, M.D., Ph.D., Julie Timsit, M.D., Gabriel Girard, Ph.D., Nicolas Lorente, Ph.D., Marie Préau, Ph.D., James F. Rooney, M.D., Mark A. Wainberg, Ph.D., David Thompson, B.C.L., LL.B., Willy Rozenbaum, M.D., Veronique Doré, Ph.D., Lucie Marchand, B.S., Marie-Christine Simon, B.S., Nicolas Etien, B.S., Jean-Pierre Aboulker, M.D., Laurence Meyer, M.D., Ph.D., and Jean-François Delfraissy, M.D. for the ANRS IPERGAY Study Group

N Engl J Med 2015; 373:2237-2246 | December 3, 2015 | DOI: 10.1056/NEJMoa1506273

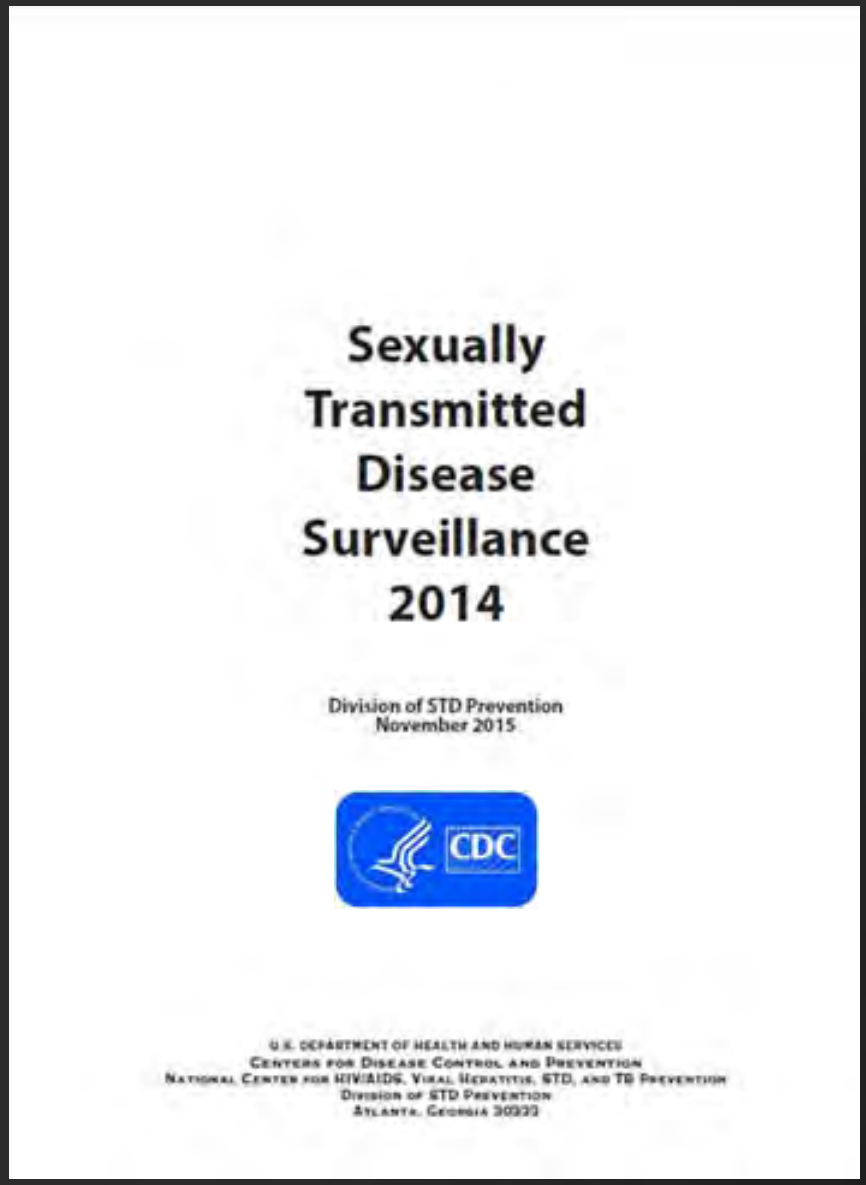
N Engl J Med 2015;373:2237-2246

Pre-exposure Prophylaxis

- Used in those with “high risk” of HIV
- Typical is to take preventative drugs DAILY
- Study: 400 gay/bisexual men divided into those who took medicine 2-24 hours before and 24 and 48 hours post unprotected sex vrs placebo at same interval
- Nine months: the use of “on demand” PrEP reduced HIV acquisition by 86%
- Side effect: GI upset (14% vrs placebo 5%)
- ***Message: persons at high risk of HIV can take PrEP on an on-demand basis, and still be protected***

N Engl J Med 2015;373:2237-2246

Sexually Transmitted Diseases



www.cdc.gov/std/stats14/surv2014-print.pdf

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

For immediate release: November 17, 2015
Contact: National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
(404) 639-8895 | NCHHSTPMediaTeam@cdc.gov

Reported Cases of Sexually Transmitted Diseases on the Rise, Some at Alarming Rate

Reported cases of three nationally notifiable STDs – chlamydia, gonorrhea, and syphilis – have increased for the first time since 2006, according to data published by the Centers for Disease Control and Prevention (CDC) in the 2014 STD Surveillance Report.

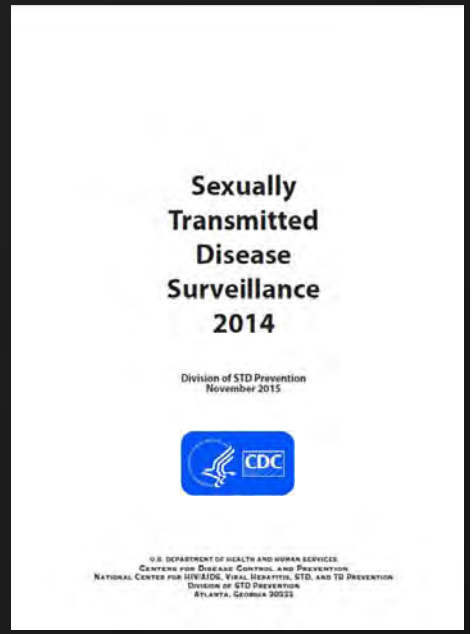
The approximately 1.4 million reported cases of chlamydia, a rate of 456.1 cases per 100,000 population, is up 2.8 percent since 2013. Rates of primary and secondary (P&S) syphilis – the most infectious stages of syphilis –and gonorrhea have both increased since 2013, by 15.1 percent and 5.1 percent, respectively. In 2014, there were 350,062 reported cases of gonorrhea (a rate of 110.7 per 100,000) and 19,999 reported cases of P&S syphilis (for a rate of 6.3 per 100,000).

STDs continue to affect young people—particularly women--most severely, but increasing rates among men contributed to the overall increases across all three diseases.

"America's worsening STD epidemic is a clear call for better diagnosis, treatment, and prevention," said Jonathan Mermin, M.D., director of CDC' Center for HIV/AIDS, Viral Hepatitis, STD, and Tuberculosis Prevention. "STDs affect people in all walks of life, particularly young women and me these data suggest an increasing burden among gay and bisexual men."

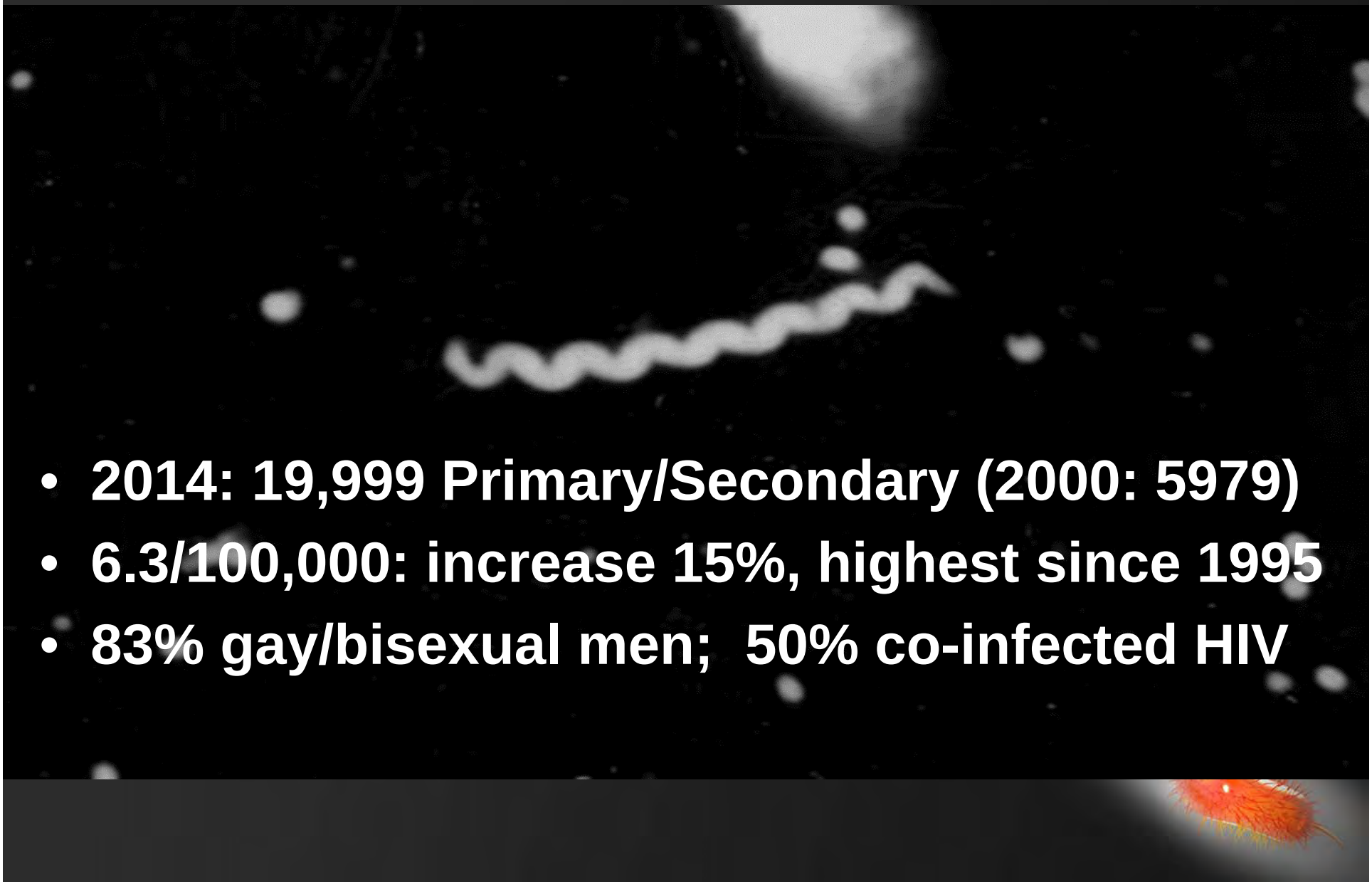
Resources

- Full Report
- Fact Sheet
- Multimedia
- Graphics



http://www.cdc.gov/nchhstp/newsroom/2015/std-surveillance-report-press-release.html

Syphilis is Resurgent!



- **2014: 19,999 Primary/Secondary (2000: 5979)**
- **6.3/100,000: increase 15%, highest since 1995**
- **83% gay/bisexual men; 50% co-infected HIV**

- Nevada (12.8 per 100,000)
- Louisiana (12.4)
- Georgia (12.3)
- California (10)
- Florida, New York and Arizona (8.9-8.7)
- Maryland (7.6)
- North Carolina (7.4)
- Oregon, Rhode Island, Illinois (6.9-6.7)
- Mississippi, South Dakota, Texas (6.3-6.2)

New Orleans
San Francisco
Las Vegas
Miami
Columbus, Ohio
Austin, Texas
San Diego
Tampa
San Antonio, Los Angeles, KC
Raleigh, NC, Orlando (all tied)
Baltimore

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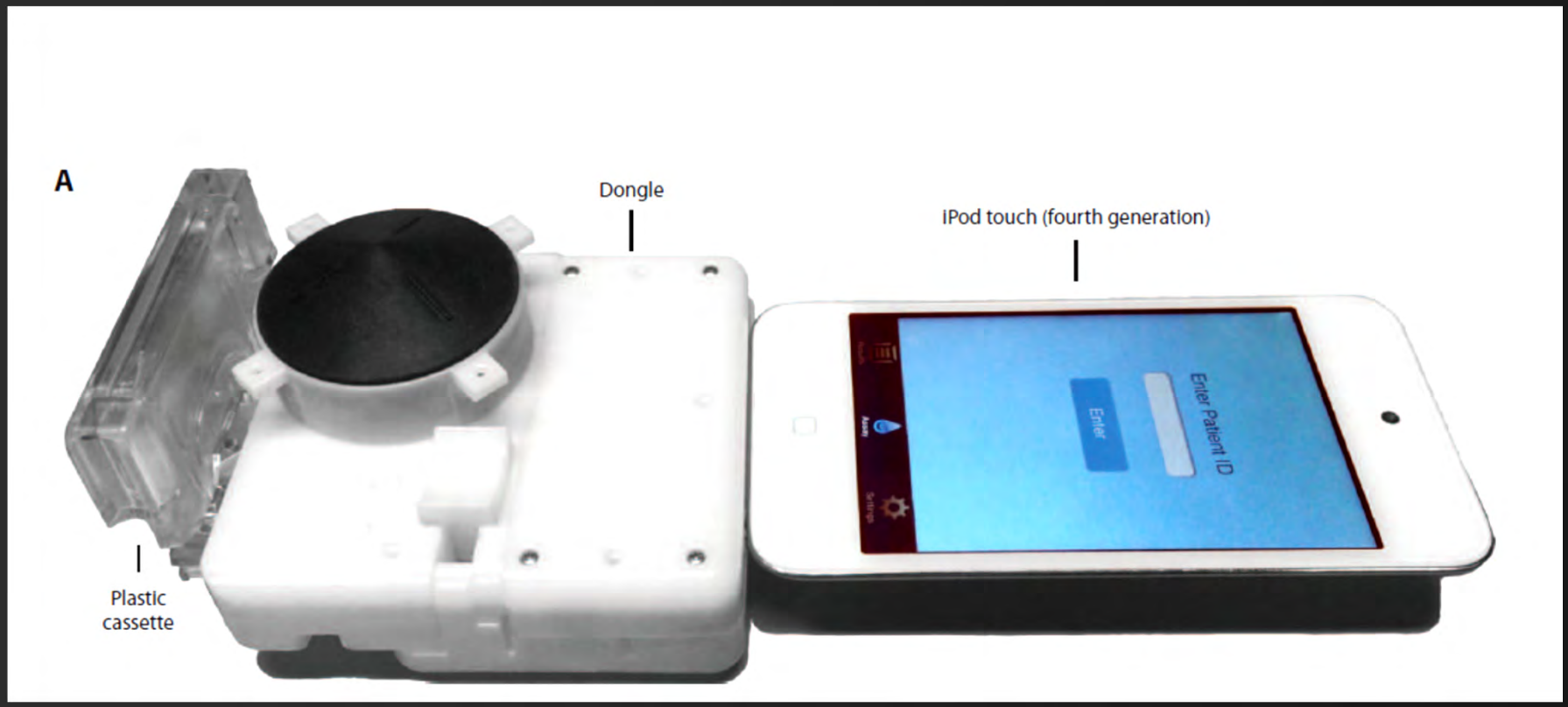


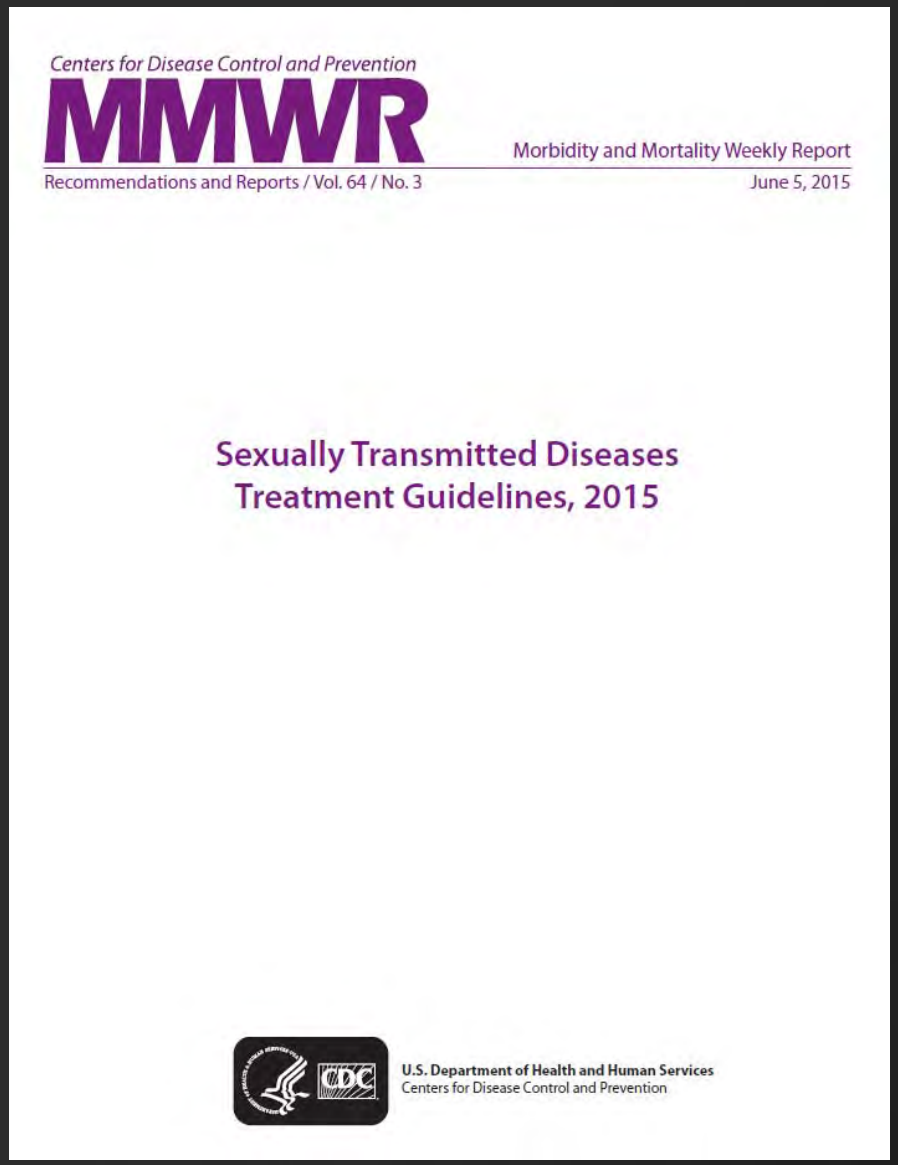
Sci Transl Med. 2015 Feb 4;7(273):273re1.

There's an APP for that!

- Fingerstick blood drop on disposable cassette
- Cassette costs $1.44 for triplex analysis
  - HIV, Treponemal and Non-treponemal tests
- Cassette inserted in dongle (ELISA tests run)
- Dongle unit (costs $34)
- Dongle hooked to audio jack of smartphone
  - Phone supplies all power required to run dongle
  - 2.4% phone batter per test: 41 tests per phone charge
- Result sent to cellphone pre-loaded app (15 min)
- HIV: Sensitivity 100%, Specificity 91%
- NTP: Sensitivity 80%, Specificity 82%
- Treponemal: Sensitivity 77%, Specificity: 89%

Sci Transl Med. 2015 Feb 4;7(273):273re1.

New STD Treatment Guidelines CDC



NO major changes of note for cutaneous STDs, except addition of 3.75% imiquimod to Rx list (along with 5%) for EGW

Dosage: QD x 2 mo

Complete clearance: ~30%

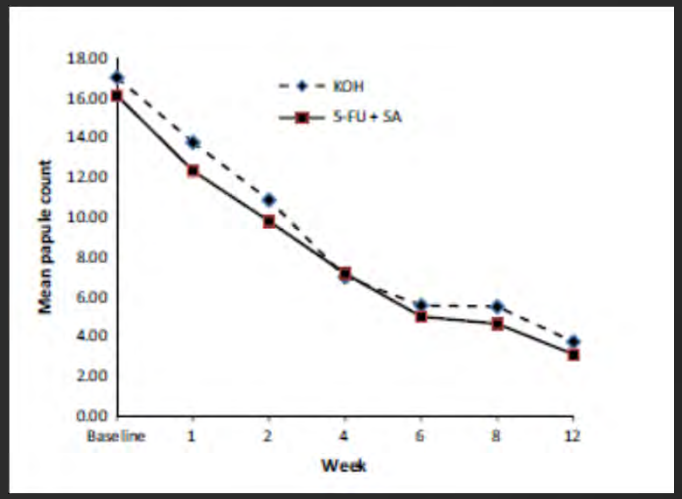
MMWR 2015;64:3, June 5, 2015

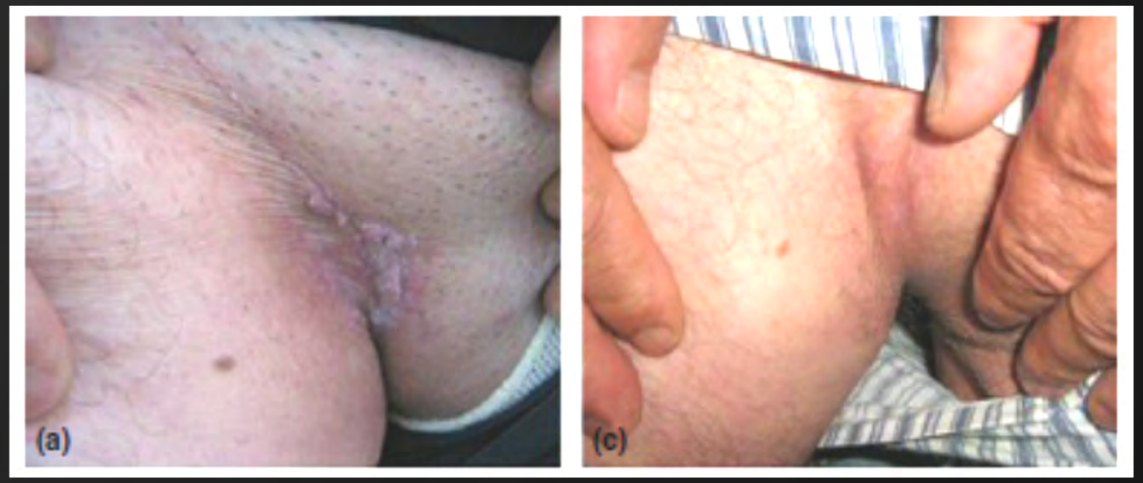
Genital Warts From Hell

TWO NEW IDEAS!

Genital Warts From Hell: Idea #1

- **Application of 5% KOH daily x 12 weeks**
- **Trial versus commercial 0.5% 5-FU-Salicylic acid 10%**
- **(Similar to USA compounded WARTpeel® 2% 5-FU, Salicylic Acid 17%)**





Clear or almost clear: 70%

Int J Dermatol 2014;53:1145-50

Genital Warts From Hell: Idea #2

- Application of ingenol mebutate
- Either 0.015% or 0.05% ONCE
- ONE APPLICATION
- Small study (n=10) all EGW at least 6 mos duration
- All verified by histology; All were HPV6+ by PCR
- Placebo gel (vehicle) controlled
- All warts cleared within 3-7 days where treated with active; No sites treated with vehicle cleared
- No recurrence in 3 months at sites which cleared
- Mild to moderate burning x 1-2 days
- Confirmatory case (More AEs)

J Invest Dermatol 2014;134:S90-107
Hautarzt 2015;66:223-5

Louis Pasteur - 1884

“When meditating on a disease, I never think of finding a remedy for it, but instead, a means of preventing it.”

New HPV Vaccine

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

A to Z Index | Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterin

News & Events

Home > News & Events > Newsroom > Press Announcements

FDA News Release

FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV

For Immediate Release December 10, 2014

New HPV Vaccine


U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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FDA News Release

FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV

For Immediate Release

December 10, 2014

- Includes VLP to immunize against HPV 6,11,16,18…and
- **Added: 31,33,45,52,58**
- Increases protection against oncogenic HPV that cause 90% vulvar, vaginal, cervical and anal carcinoma
- Protection efficacy rate: 99% EGW, 97% genital SCCA 75% anal SCCA
- Three injections (0,2,6 mo)
- F 9-26yo M 9-15yo (older MSM)

Cancer Epidemiol 2014;38:748-56

New 9vHPV Vaccine

- If vaccination series NOT complete, may do so with either quadrivalent or nanovalent vaccine
- If vaccination series with 4vHPV is complete, NOT recommended to do series of 9vHPV due to not being “cost-effective”
- Cost $100,000 for quality-adjusted 1 year of life
- ***Manufacturer will be discontinuing quadrivalent vaccine by end of 2016***
- Safety: ~10% increased risk of injection site reactions: pain, erythema, swelling with 9vHPV

J Natl Cancer Inst. 2015 Apr 29;107(6)

Anti-HPV Vaccine Propaganda

Acta Derm Venereol 2015 Preview

SHORT COMMUNICATION

Quadrivalent Human Papillomavirus Vaccination: A Promising Treatment for Recalcitrant Cutaneous Warts in Children

Dietrich Abeck[1] and Regina Fölster-Holst[2]

[1]Group Practice for Dermatology and Allergology, Renatastrasse 72, DE-80639 München, and [2]Department of Dermatology and Allergology, University Kiel, Lübeck, Germany. E-mail: professorabeck@mytum.de

Accepted Mar 30, 2015; Epub ahead of print Mar 31, 2015

Cutaneous human papillomavirus (HPV)-induced warts are common in the general population, especially among children. Prevalence rates among primary schoolchildren are between 22% and 33% (1). In childhood, in particular, the spontaneous resolution rate of HPV-induced warts is high. Half of primary schoolchildren will be free of warts within one year (2) and approximately two-thirds of warts clear without treatment within 2 years (3). However, dermatologists still see a high number of children with extragenital warts that do not resolve spontaneously for years and cause psychological (particularly if located on the hands and fingers) and physical (pain and irritation if located sub- or peri-ungually) problems. At present a large number of different approaches to treat these

Administration of the vaccine was therefore started. The vaccine was administered in 3 separate intramuscular injections in the deltoid region of the upper arm. Permission was obtained from parents and referring paediatricians. The vaccine is licensed for use at 9 years of age and over in Germany. No other vaccination regime was performed 4 weeks prior to this treatment, during the active vaccination process and 4 weeks afterwards.

RESULTS

The vaccine was well-tolerated, with local swelling, lasting only for a short time, in some children. In 4 children healing of warts was documented between the 2nd and 3rd vaccination, 1 girl was disease-free after

Acta Derm Venereol. 2015;95:1017-9

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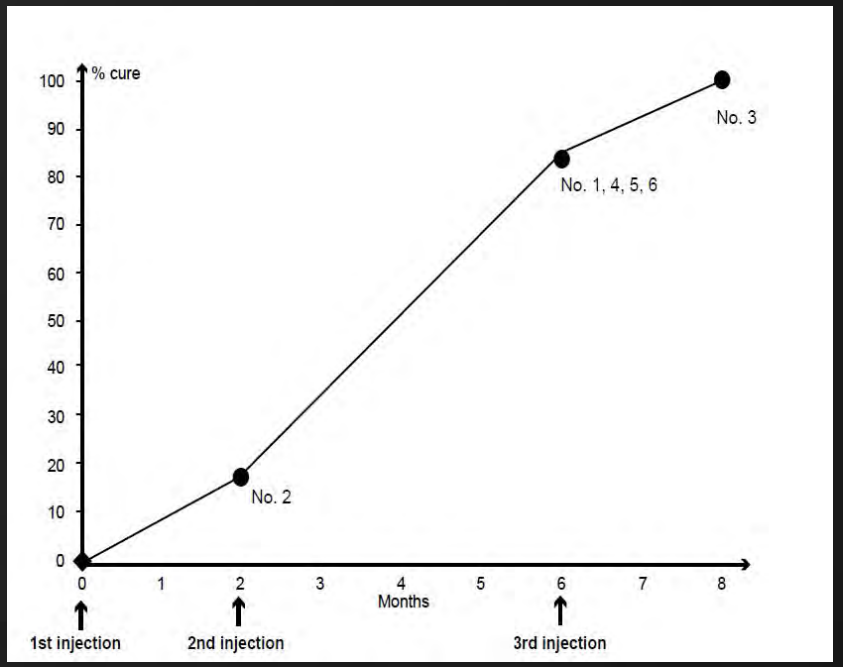
Acta Derm Venereol. 2015;95:1017-9

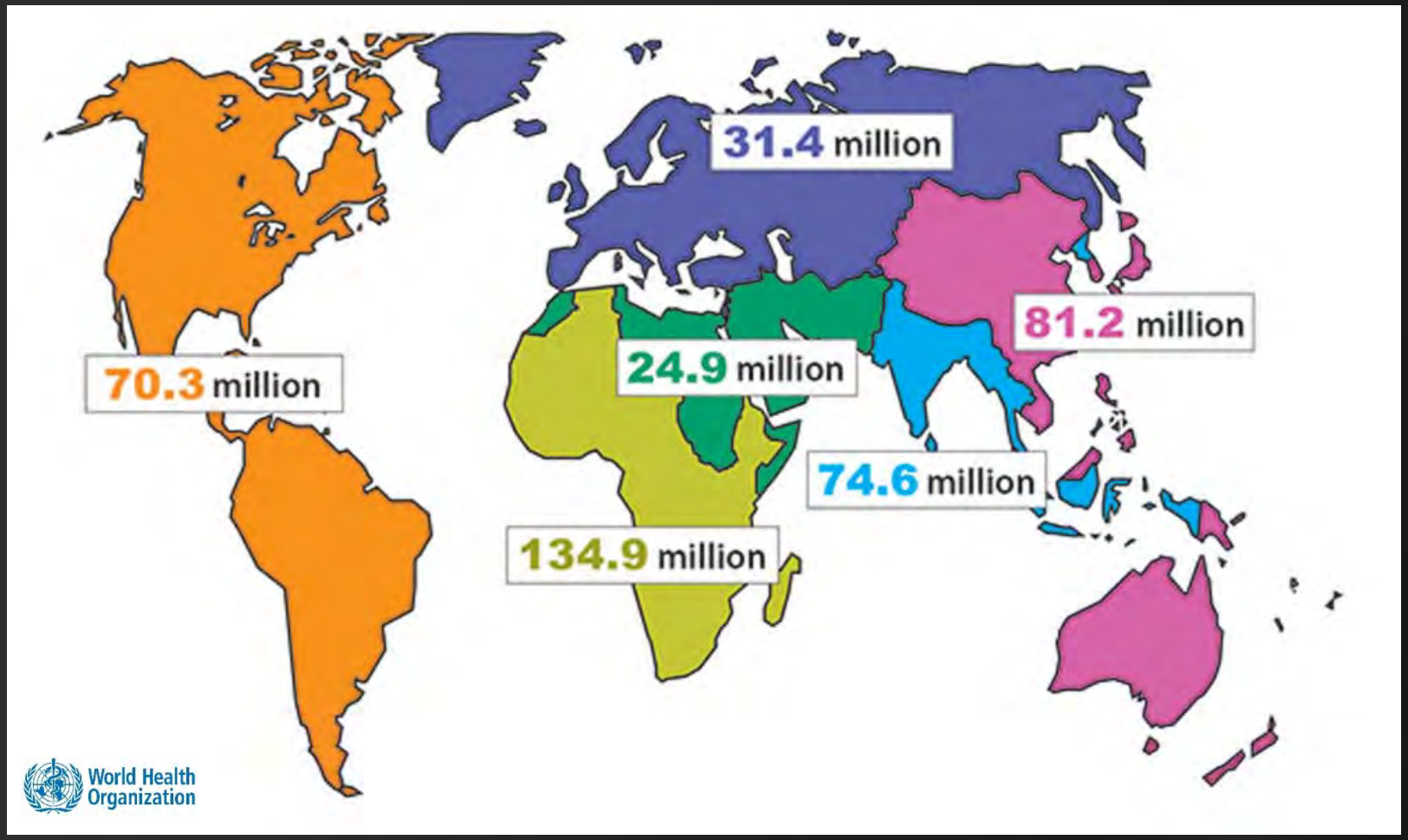
Quadrivalent HPV Vaccine Rx for Extragenital Cutaneous Warts

- Six children 9-11yo
- Recalcitrant warts: palmar or plantar or both
- Failed: Salicylic acid, Duct tape, Cryo LN_2, Imiquimod, 5-FU, CO_2 laser, Cimetidine
- QV HPV x 3 shots
- ALL clear warts



Acta Derm Venereol. 2015;95:1017-9

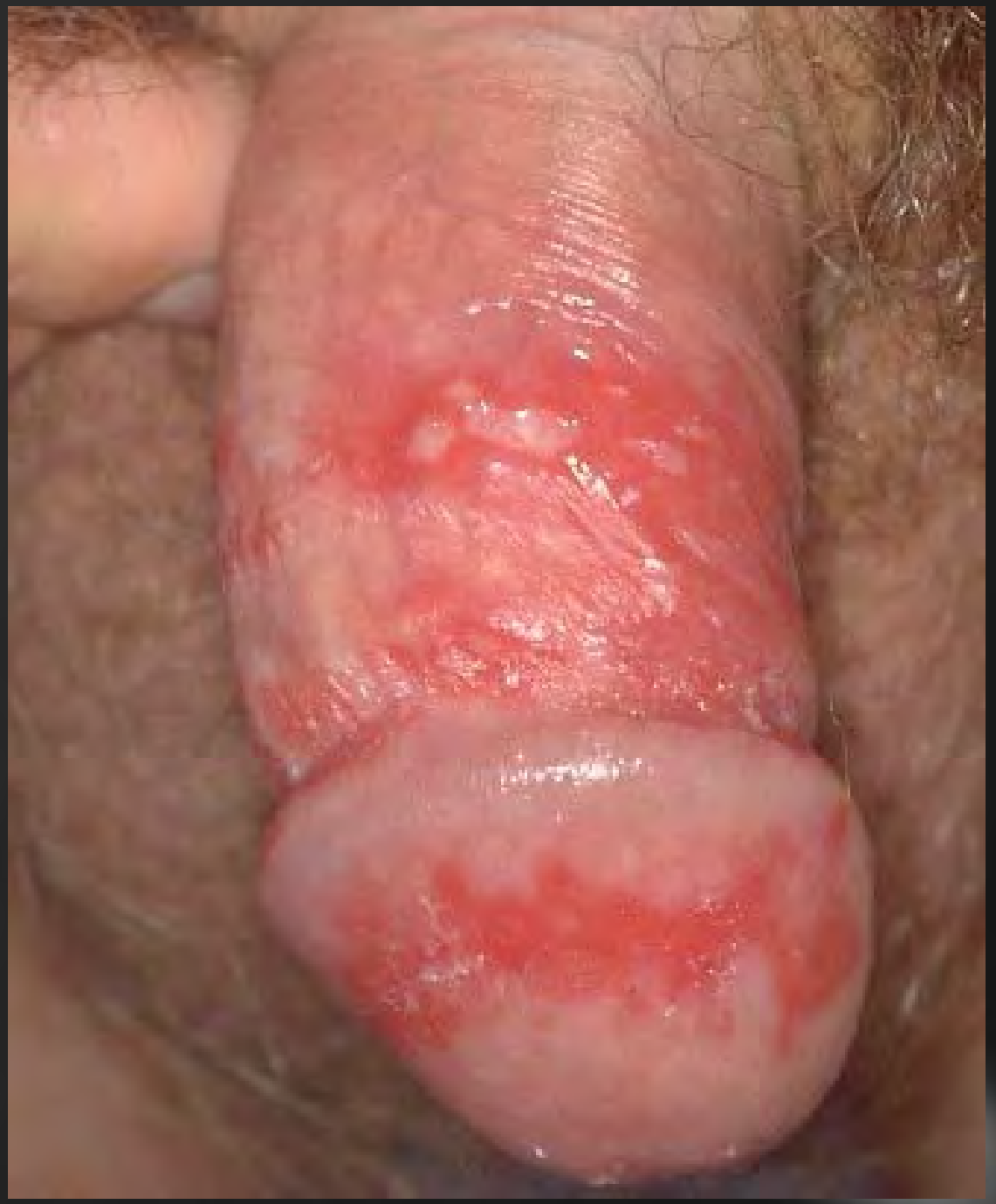
Global HSV-2 Prevalence



267 x 10^6 ♀
150 x 10^6 ♂
19 x 10^6 NEW infections/year

PLoS One. 2015 Jan 21;10(1):e114989

HSV-2



Thermotherapy Genital Herpes

- German prospective study; 32 women; mean age 35 yo
- 21 ThermoRx + Acyclovir, 10 ThermoRx alone
- Treatment initiated w/ first objective sign HSV-2
- Within one day, Sx gone or almost gone, with or without acyclovir as concomitant therapy
- ThermoRx done with handheld device (administers 51-53^{0}C for 4 seconds) 1-2x daily

Clin Cosmetic Investig Dermatol 6:163-66, 2013

Approved device in UK, EU, Australia, Canada, several Latin American countries;
Available on either E-Bay or Amazon

Genital Herpes: New Rx?

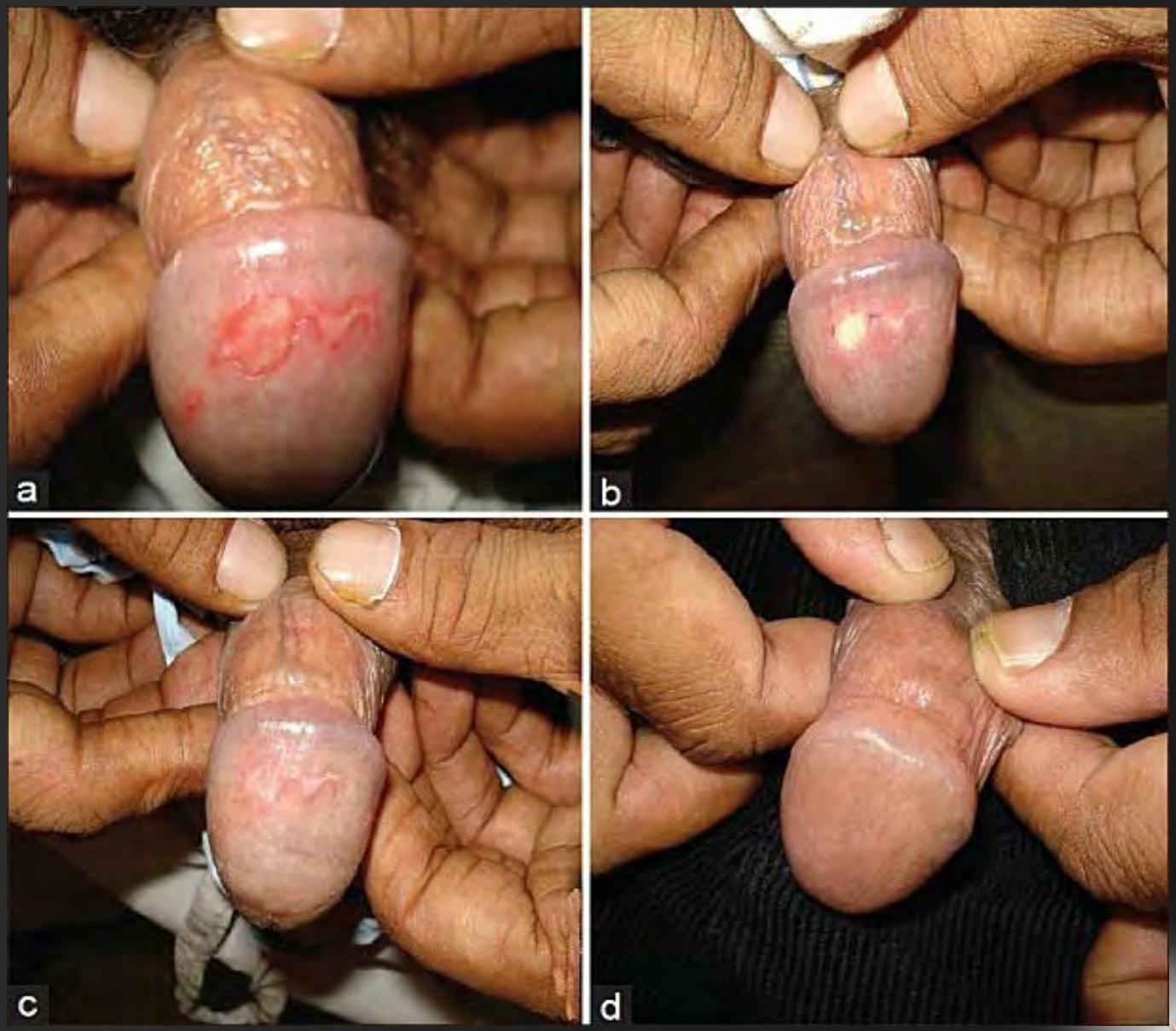
- **Topical zinc sulfate**
- **Zn^{+2} in-vitro impairs HSV growth**
- **Can zinc salt treat active genital HSV?**
- **Can zinc salt reduce recurrence rate?**
- **100 clinical + Tzanck verified men with genital HSV treated for 6 months**
- **To active lesion (or area): Q5d x 1mo, then Q10d x 2 mo, then Q15d x 3 mo**
- **$ZnSO_4$ solution; 5 minute exposure**

Indian J Sex Transm Dis. 2013;34: 32–34

Genital Herpes: New Rx?

	Recurrence rate over 6 months
Distilled water control	80%
1% Zinc sulfate	33.33%
2% Zinc sulfate	20%
4% Zinc sulfate	3.33%

Indian J Sex Transm Dis. 2013;34: 32–34



Indian J Sex Transm Dis. 2013;34: 32–34

Scabies and Ivermectin

Small study (n=62) done in Egypt; Randomized but not sham controlled
Oral Ivermectin 200ug/kg versus single application 1% ivermectin solution
M=F in all groups; age >5 and weight >15kg
Rx repeated once if SYMPTOMS persist in one week
Clinical success: no itching, no rash, negative microscopy

WEEK	TOPICAL IVERMECTIN % Itch and lesion free	ORAL IVERMECTIN % Itch and lesion free
1	87.5	73.5
4	100	100

Not statistically significant

Dermatol Ther. 2016;29:58-63

Topical Ivermectin?

- In the United States, we have (for human use) oral ivermectin and NO ivermectin solution
- However, we DO have 1% ivermectin cream, approved for the treatment of rosacea

J Eur Acad Dermatol Venereol. 2015; Dec 21. doi: 10.1111/jdv.13537. [Epub ahead of print]

J Drugs Dermatol. 2014;13:316-23 and 2014;13:1380-6

Scabies and anti-TNF Biologic Drugs

Etanercept
J Am Acad Dermatol. 2013 Apr;68(4):e138-92005

Infliximab
J Am Acad Dermatol. 2005 Apr;52(4):719-20

Adalimumab
Acta Dermatovenerol Croat. 2015;23(3):195-8
Infect Control Hosp Epidemiol. 2015 Nov;36(11):1358-60

I hope you've enjoyed hearing about STDs!

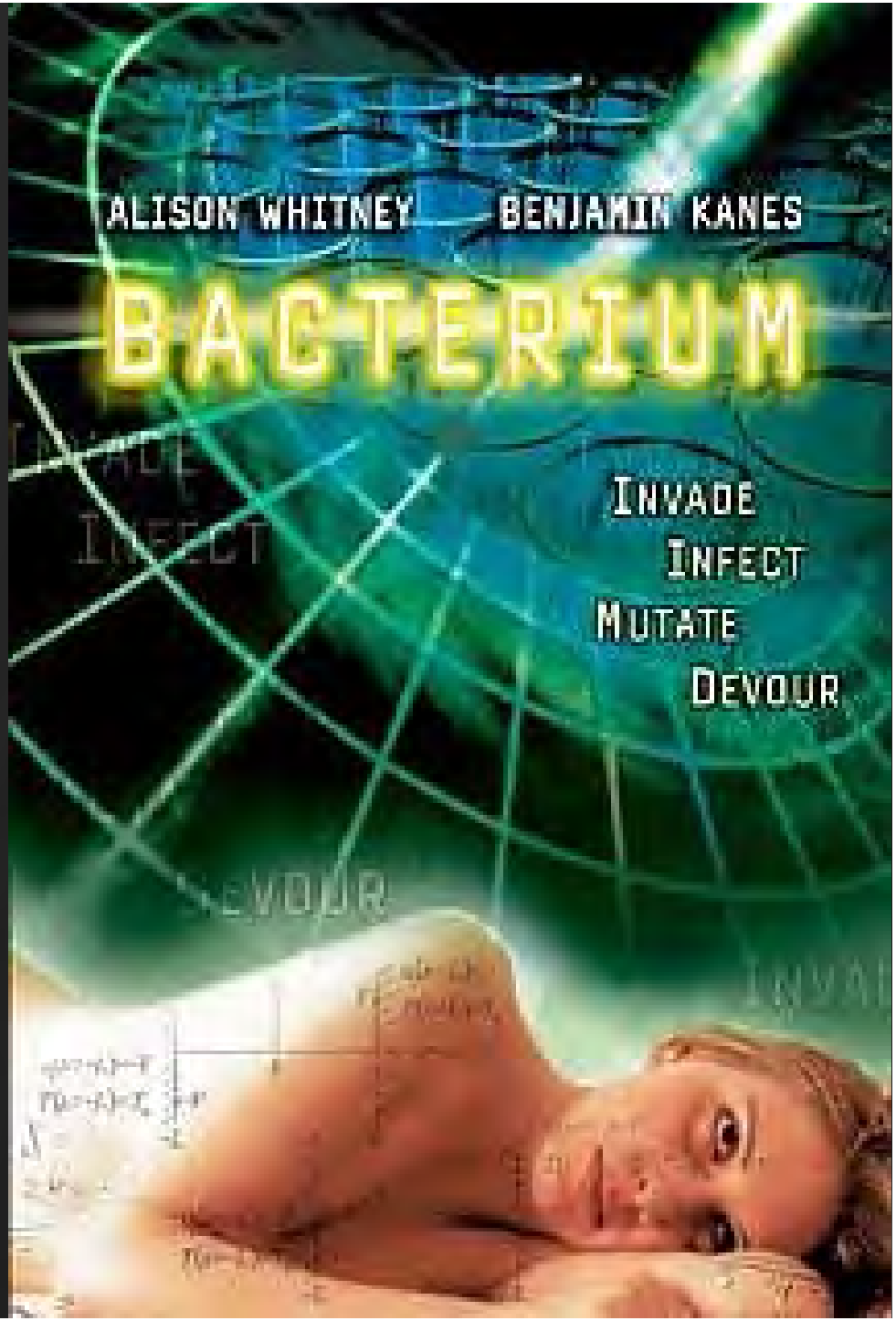
Before changing topics, I will leave you with two conflicting views about sex…

View of Sex: #1

1. Relieves Stress
2. Boosts Immunity
3. Burns Calories
4. Improves Cardiovascular Health
5. Boosts Self-Esteem
6. Improves Intimacy
7. Reduces Pain
8. Reduces Prostate Cancer Risk
9. Strengthens Pelvic Floor Muscles
10. Helps You Sleep Better

View of Sex #2

BACTERIA

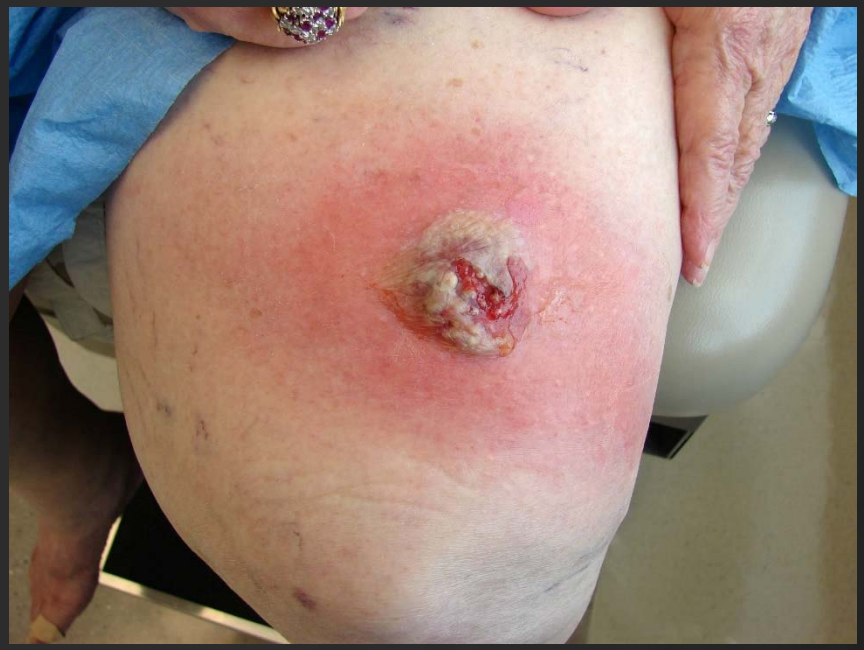

ALISON WHITNEY
BENJAMIN KANES
BACTERIUM
INVADE
INFECT
MUTATE
DEVOUR

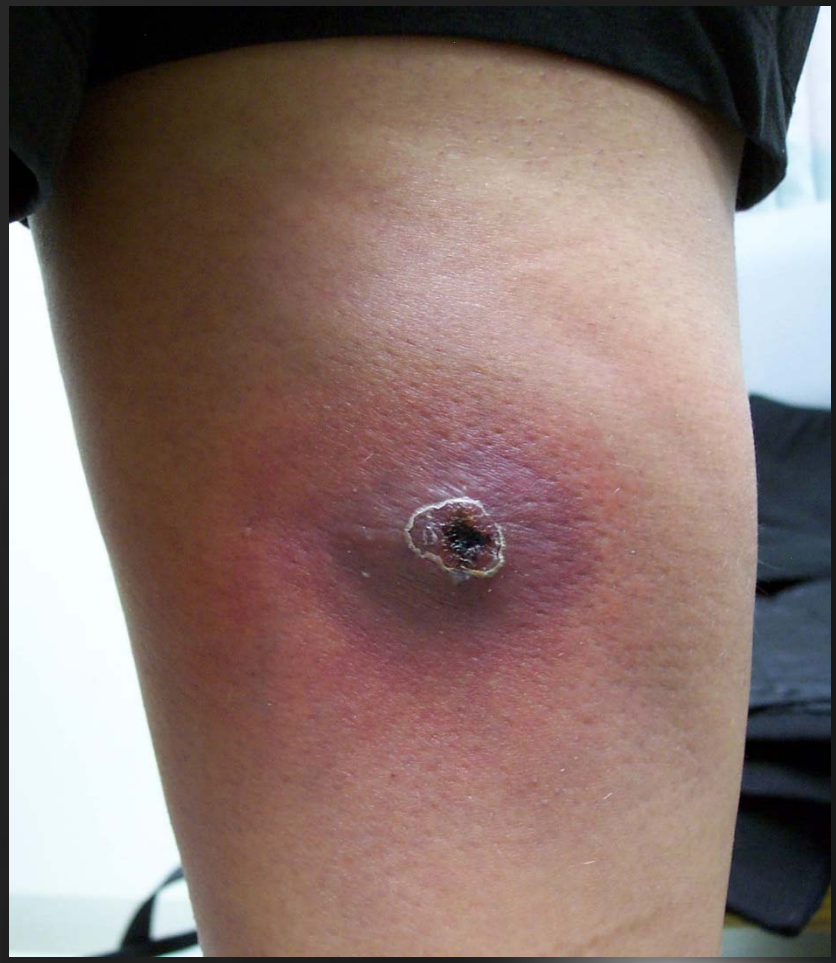
MRSA: USA 300

- Athletes, prisoners, military personnel, IVDU, MSM, homeless; ALSO most common general population
- Unlike HA-MRSA, uniquely capable of colonizing extra-nasal sites (oro-pharyngeal, anogenital) and survive on fomites
- Increasingly multi-drug resistant, including possible mupirocin resistance
- Invariably PVL+ (unlike MSSA and HA-MRSA); Does PVL confer virulence? Unknown
- Clinically: Abscess and cellulitis

Antimicrob Agents Chemother 2010; 54: 3804–3811
J Antimicrob Chemother 2009; 64: 441–446
Ann Intern Med 2006;144: 309–317
Cutis 2006;77: 229-32

USA 300 MRSA





Smoking and MRSA

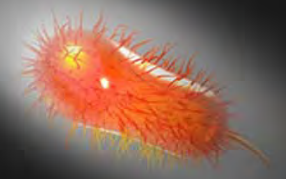
- MRSA exposed to cigarette smoke, dose dep
  - Change surface charge (more positive by 5-11x)
  - Increase hydrophobicity by 55%
- > Resistance to macrophage killing (4x survival)
- > Resistance to killing by ROS
- < Susceptibility to cell lysis (1.78x less)
- Impaired binding of AMP (Increased MBC by 2x)
- Increased keratinocyte adherence (2x)

Infect Immun 2015;83:2443-52

Moral: Hard To Eradicate MRSA…

Recurrent Bouts of MRSA: Source?

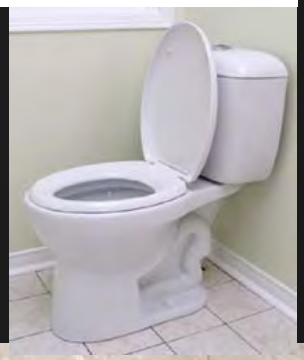
- **Patient: autoinoculation** (nares, throat)
- **Family members**
  Epidemiol Infect 2014;April 24 pages 1-12 (e-pub)
- **Sex partner** (heterosexual or homosexual)
  Int J STD AIDS 2012;23:524-6
- **Pets** (dog or cat)
  Vet Dermatol 2012;23:267-75
- **Food** (raw, as sold in the grocery store)
  Food Microbiol 2014; 42:56-60
- **Household Environment**
  Infect Control Hosp Epidemiol 2014;35:1373-82

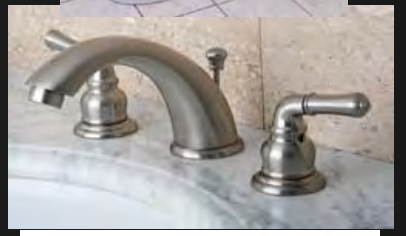


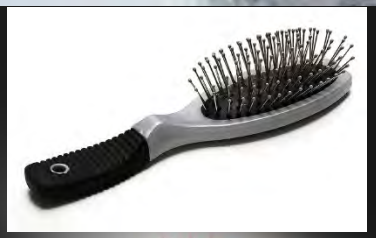
This talk dedicated to:
Smog Rosen 1994-2014

MRSA: Household Environment

- Investigation 346 households w/ a proven index case of MRSA
- Los Angeles and Chicago
- High rates of initial and persistent (3 mo) MRSA colonization were: landline phone, bathroom toilet and sink faucet, hairbrush; Less: kitchen faucet & counter, television remote, refrigerator door
- MRSA300 58% initial and 63% at 3 mo
- *"Persistent reservoir placing all household members at risk for MRSA infection"*

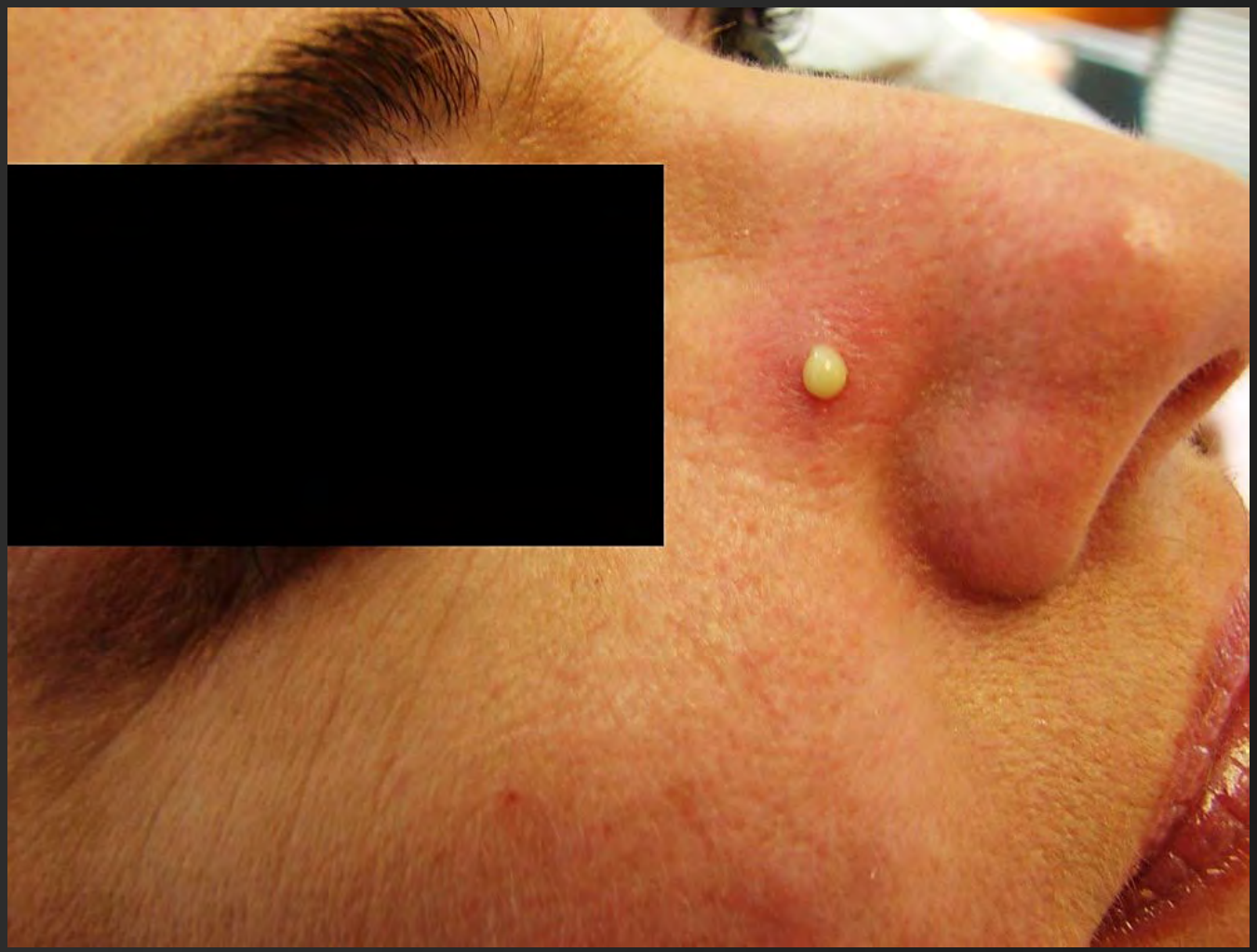






Infect Control Hosp Epidemiol 2014;35:1373-82

MRSA: Therapy



INTRAVENOUS MRSA AGENTS
NEW APPROVED DRUGS!

NAME	CHEMICAL CLASS
Vancomycin	Glycopeptide
Daptomycin	Lipopeptide
Linezolid	Oxazolidinone
Telavancin	Glycopeptide
Ceftaroline	Cephalosporine
Quinupristin-Dalfopristin	Streptogramin
Oritivancin	Glycopeptide
Dalbavancin	Glycopeptide
Tedizolid	Oxazolidinone

NAME	CHEMICAL CLASS
Vancomycin	Glycopeptide
Daptomycin	Lipopeptide
Linezolid	Oxazolidinone
Telavancin	Glycopeptide
Ceftaroline	Cephalosporine
Quinupristin-Dalfopristin	Streptogramin
Oritivancin *Approved: 8-6-2014*	Glycopeptide
Dalbavancin *Approved: 5-23-2014*	Glycopeptide
Tedizolid *Approved 6-20-2014*	Oxazolidinone

NAME	T1/2 (Hour)	ADULT DOSE	ROUTES AVAILABLE
Vancomycin	5-11	500mg Q6h 1000mg Q12h	IV (PO)
Daptomycin	8	4-6mg/kg Q24h	IV
Linezolid	4-5	600mg Q12h	IV, PO
Televancin	8	10mg/kg Q24	IV
Ceftaroline	~3	600mg Q12h	IV
Quinupristin-Dalfopristin	1-3	7.5mg/kg Q12h	IV
Oritivancin	245	1200mg Single dose	IV
Dalbavancin	150-250	1000mg; 500mg one week later	IV
Tedizolid	8-12	200mg QD	IV, PO

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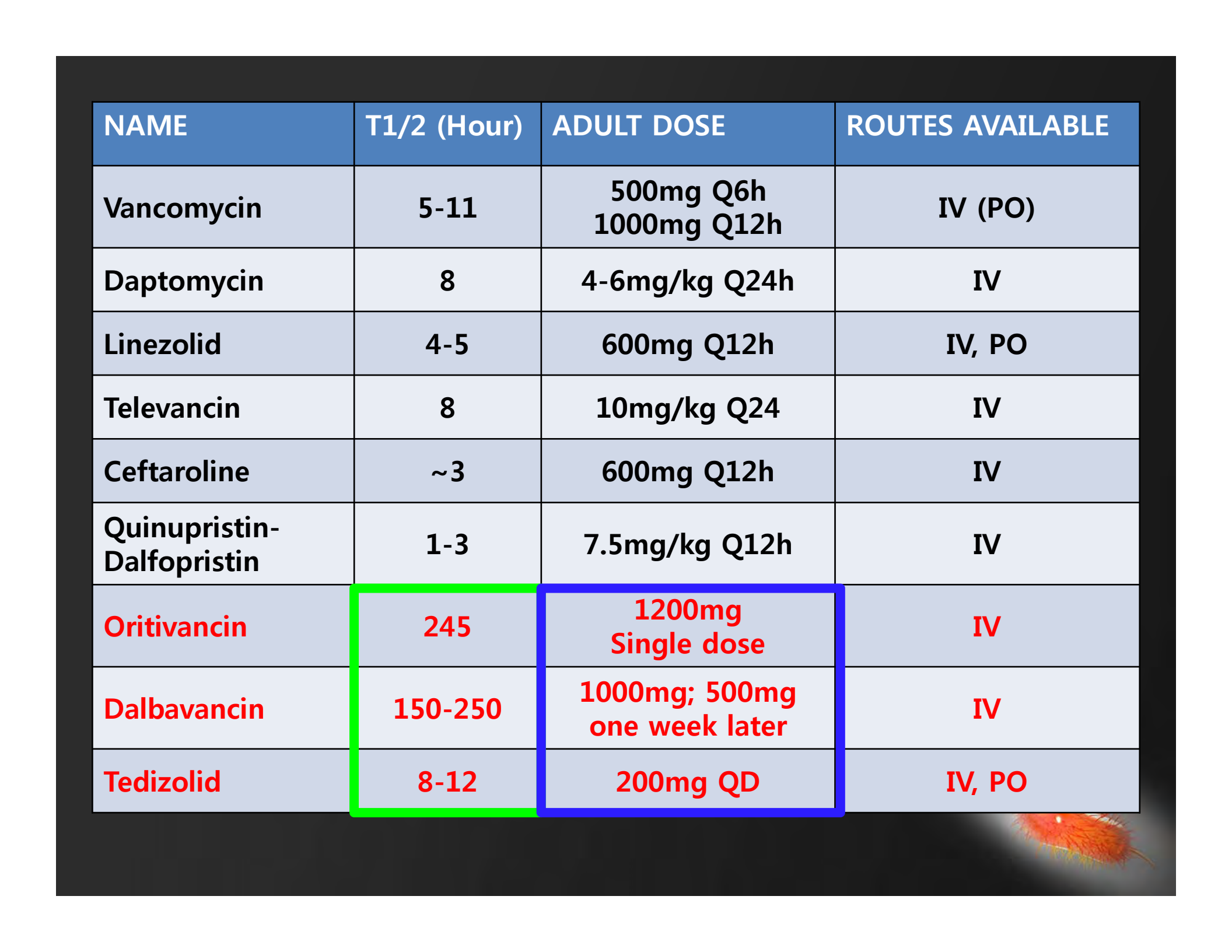
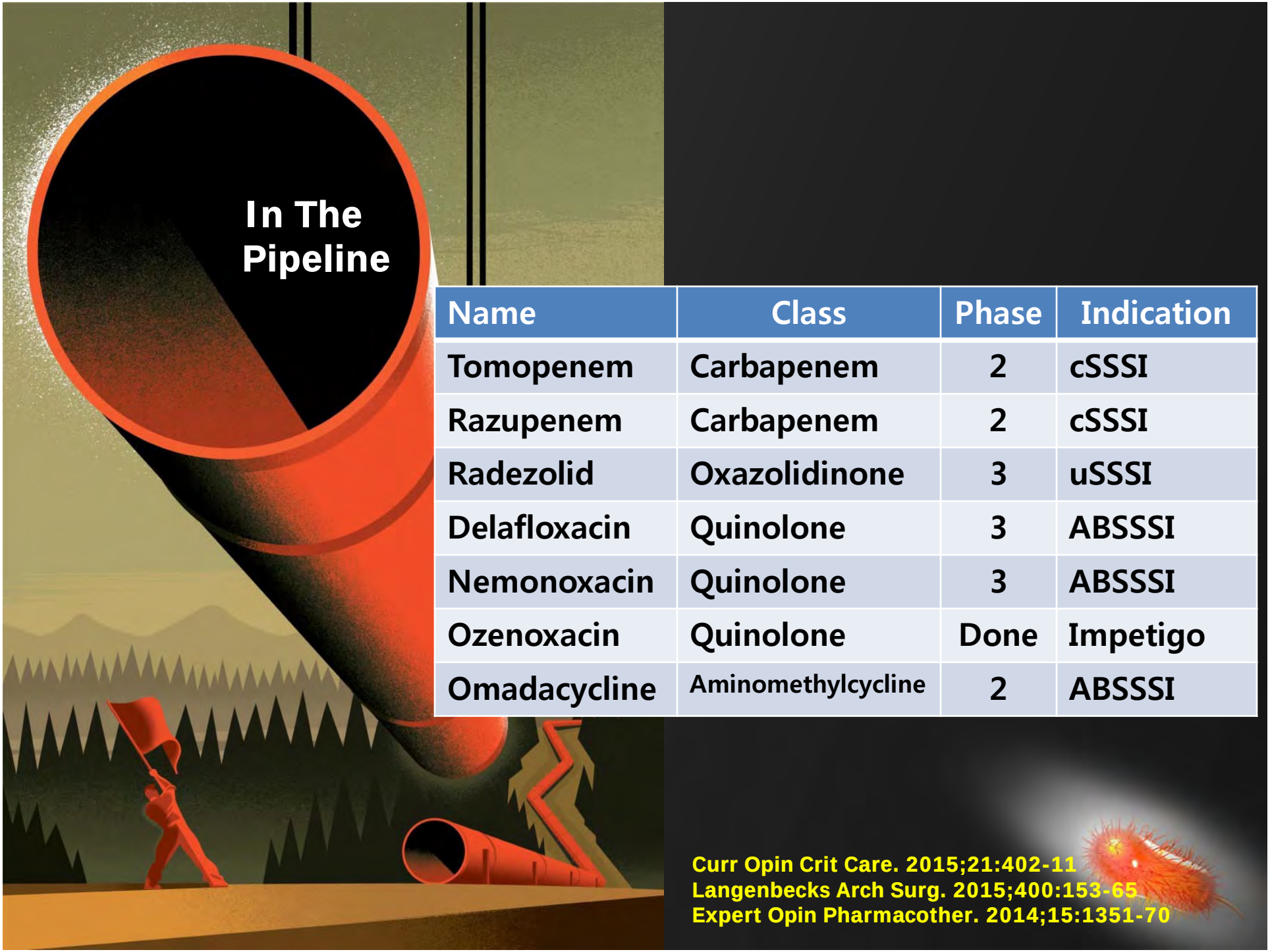


New MRSA Drugs

- **Summary**
- **J Clin Microbiol. 2016 Mar 9. pii: JCM.03395-15.**
- **Oritivancin**
- N Engl J Med 2014;370:2180-90
- **Dalbavancin**
- Clin Infect Dis. 2016;62:545-51 (Single dose 1500mg)
- Am J Health Syst Pharm 2014;71:1062
- N Engl J Med 2014;370:2169-79
- **Tedizolid:**
- Am J Health Syst Pharm 2014;71:621-33
- JAMA 2013;309:559-69



Name	Class	Phase	Indication
Tomopenem	Carbapenem	2	cSSSI
Razupenem	Carbapenem	2	cSSSI
Radezolid	Oxazolidinone	3	uSSSI
Delafloxacin	Quinolone	3	ABSSSI
Nemonoxacin	Quinolone	3	ABSSSI
Ozenoxacin	Quinolone	Done	Impetigo
Omadacycline	Aminomethylcycline	2	ABSSSI

Curr Opin Crit Care. 2015;21:402-11
Langenbecks Arch Surg. 2015;400:153-65
Expert Opin Pharmacother. 2014;15:1351-70

Ozenoxacin

- New topical antibiotic: Impetigo (1% cream)
- Quinolone
- Bactericidal: gram positives, including MRSA
- RCT versus placebo and retapamulin (n=465)
  - Age ≥ 2 months, BID x 5 days
- New criteria: Skin Infection Rating Sale (SIRS)
- Success (clinical/micro) = Retapamulin

Future Microbiol 2014;9:1013-23

VIRUS


JAMIE LEE CURTIS
WILLIAM BALDWIN
DONALD SUTHERLAND
VIRUS
Earth is in for a shock.
NOW AVAILABLE ON VIDEOCASSETTE AND DVD!

Mucoadhesive Acyclovir

- **Applied at prodrome***
- **Single tablet 50mg is therapy**
- **Massive concentration labial mucosa/saliva**
- **Reduces healing time (v. placebo) by ½ day**
  Reduces duration of episode by 1.0 day
- **Compared to placebo, 24% more episodes are aborted (no lesions develop)**
- ***?Disease modifying agent; During 9 month follow-up, increased time to next recurrence by 105 days (mean) or 40 days (median)***

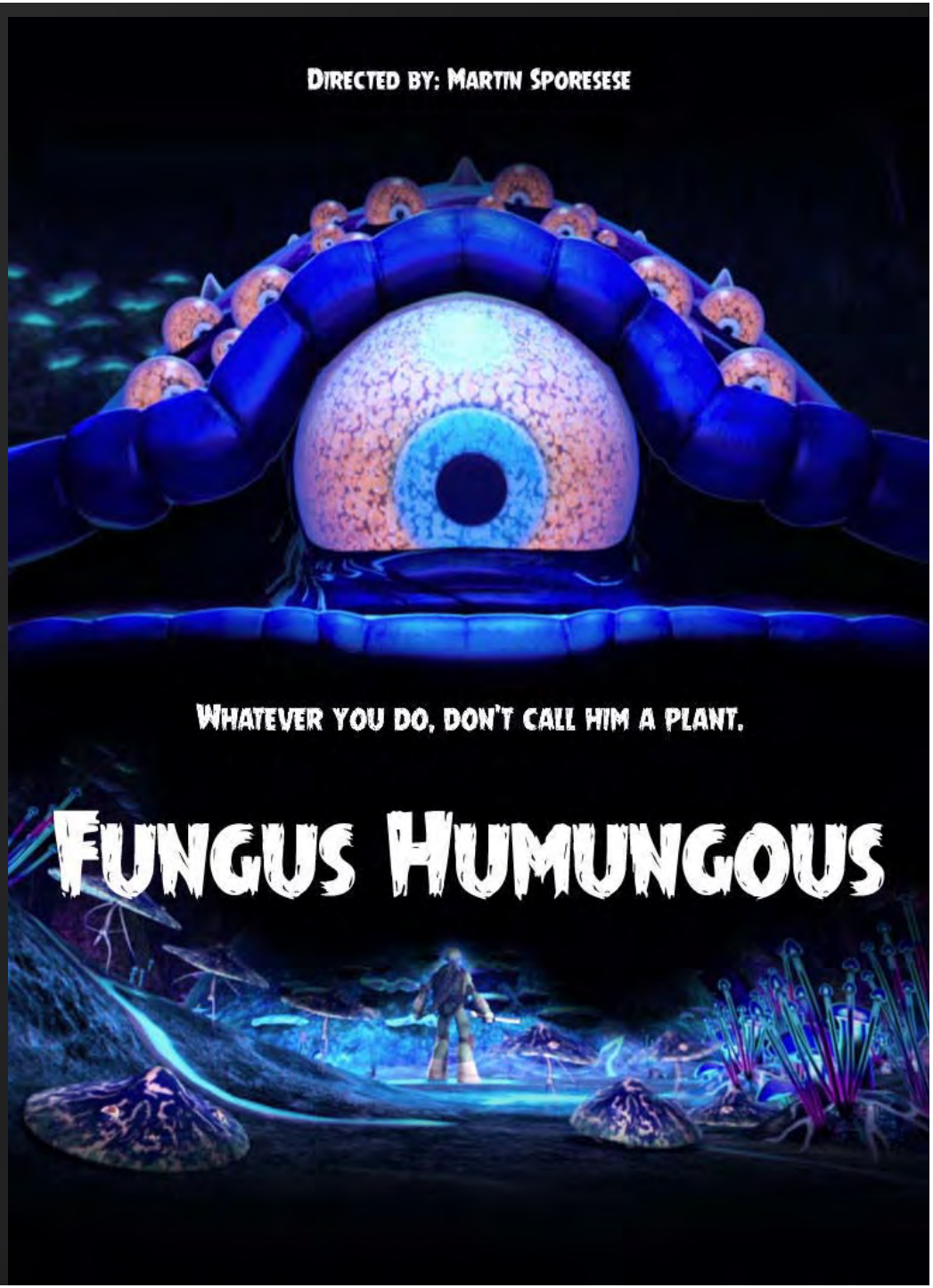
J Drugs Dermatol. 13:791-8, 2014
J Clin Pharmacol & Clin Pharmacokinet. 2014; 1(1):000001

Post-herpetic Neuralgia
Two Pearls

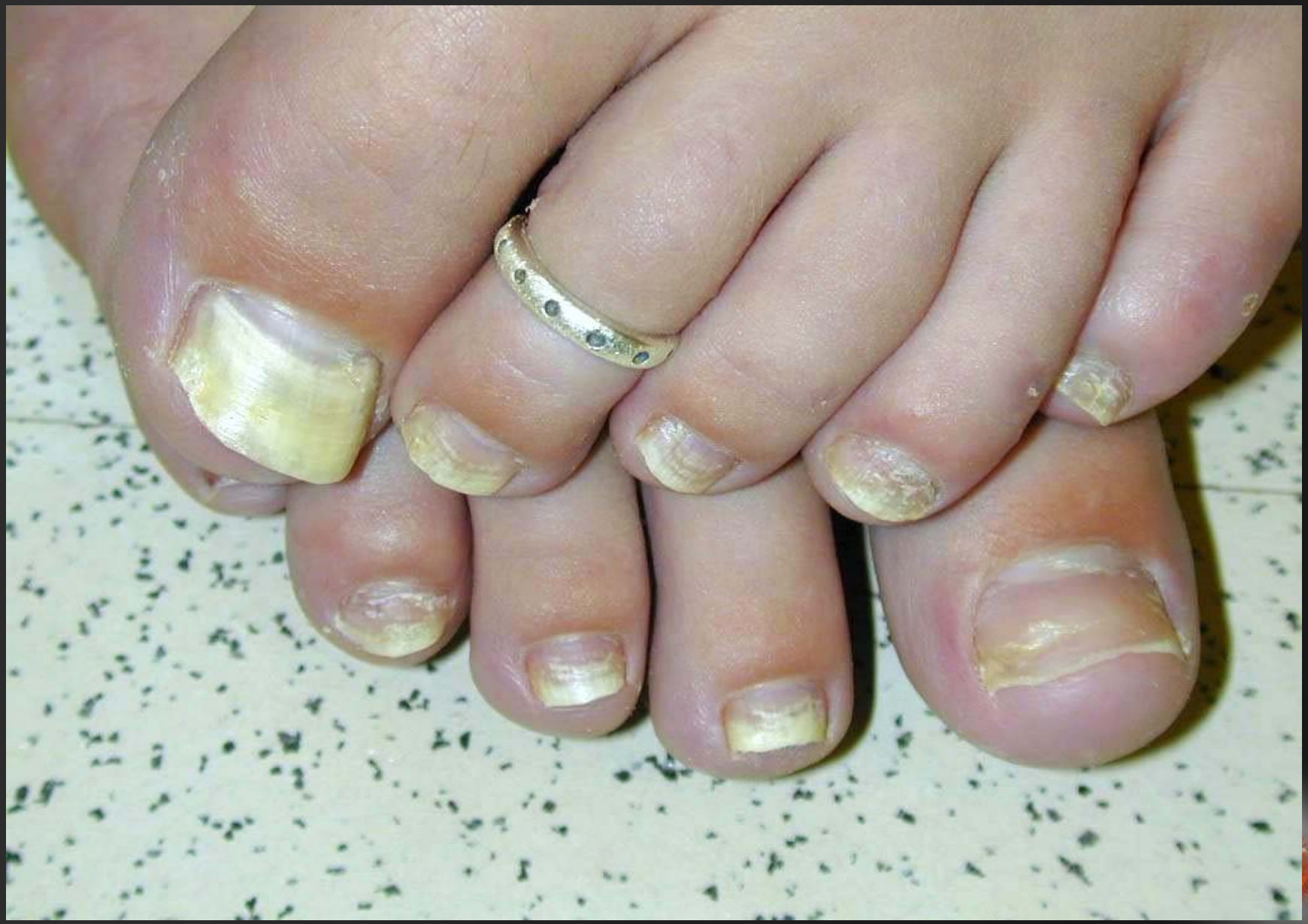
- Topical gabapentin
- Median age 83 (n=3)
- PHN for 9 months with near maximal sleep disruption
- 6% gabapentin cream applie d TID
- 2/3 responded w/ decreased pain and increased sleep
- Br J Dermatol Dec 18, 2014 e-pub

- “Cryoanalgesia”
- Liquid nitrogen sprayed al ong affected dermatome
- Distance 6 inches
- Spray for 30 seconds
- Weekly; mean number =3
- 94% good to excellent pain relief by sixth treatment
- Int J Dermatol 50:746-50, 2011

FUNGI


Directed by: Martin Sporesese
Whatever you do, don't call him a plant.
Fungus Humungous

Onychomycosis: Expanded Rx Options



More Onychomycosis?

Onychomycosis: Therapy

AGENT	COMPLETE CURE (Almost Complete Cure)	MYCOLOGIC CURE
Terbinafine	38% (59%)	70%
Itraconazole	14% (35%)	54%
Ciclopirox 8%	7.0% (9.3%)	33.0%
Almost complete cure is:	≤ 5%-10% residual abnormal nail with	mycologic cure

All data based on package insert

Onychomycosis: Therapy

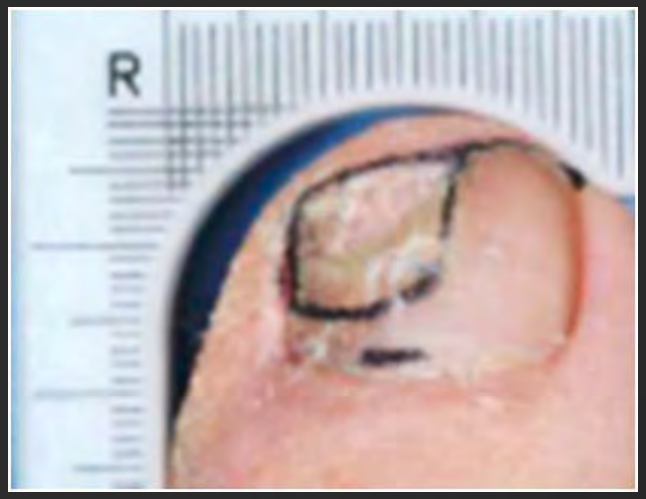
AGENT	COMPLETE CURE (Almost Complete Cure)	MYCOLOGIC CURE
Terbinafine	38% (59%)	70%
Itraconazole	14% (35%)	54%
Ciclopirox 8%	7.0% (9.3%)	33.0%
Efinaconazole 10%	16.5% (24.9%)	54.3%
Tavaborole 5%	7.8% (16.6%)	33.5%
Almost complete cure is:	≤ 5%-10% residual abnormal nail with	mycologic cure

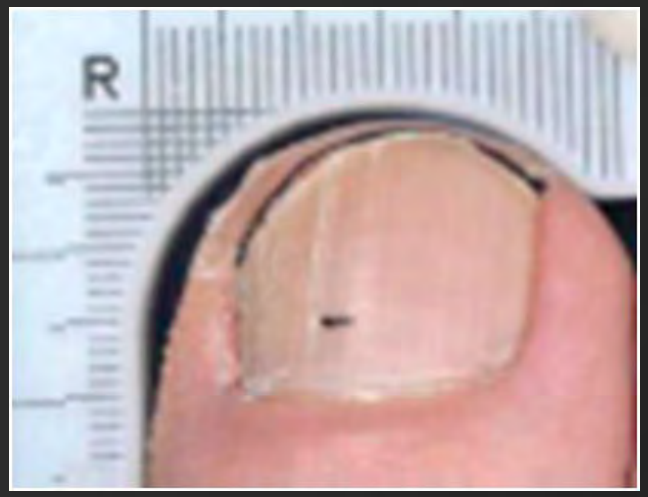
All data based on package insert

Efinacolnazole: J Am Acad Dermatol. 2013;68:600-608
Tavaborole: J Clin Aesthet Dermatol. 2014;7:13-21

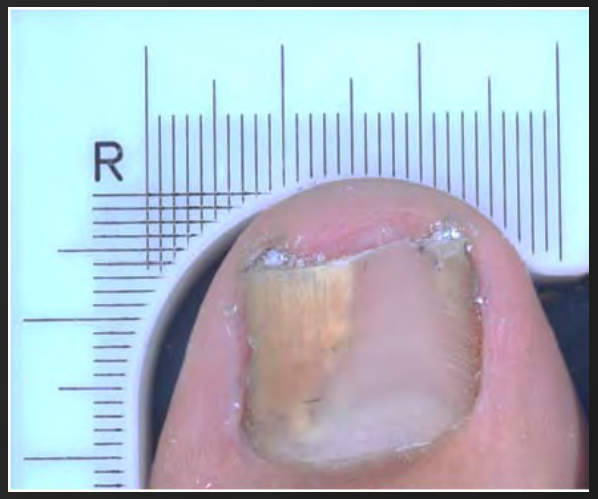
Before and After….

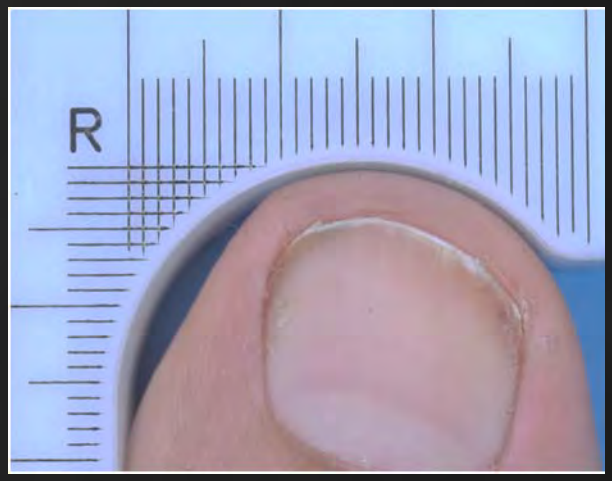
Efinaconazole





Tavaborole

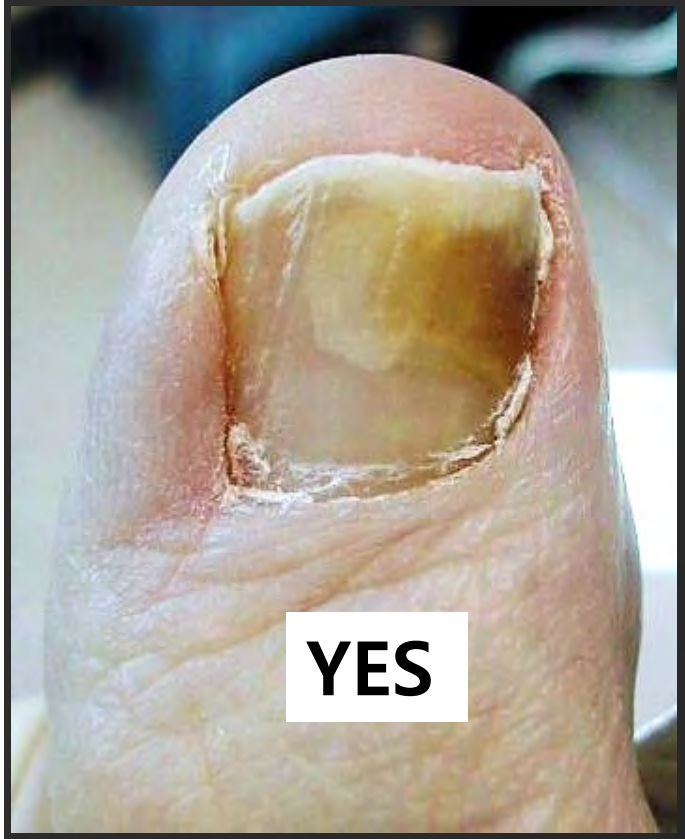


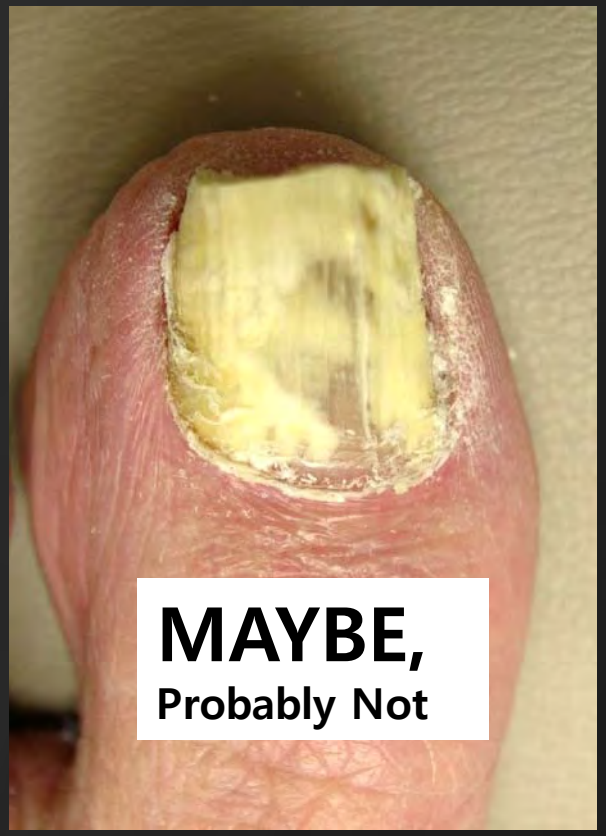


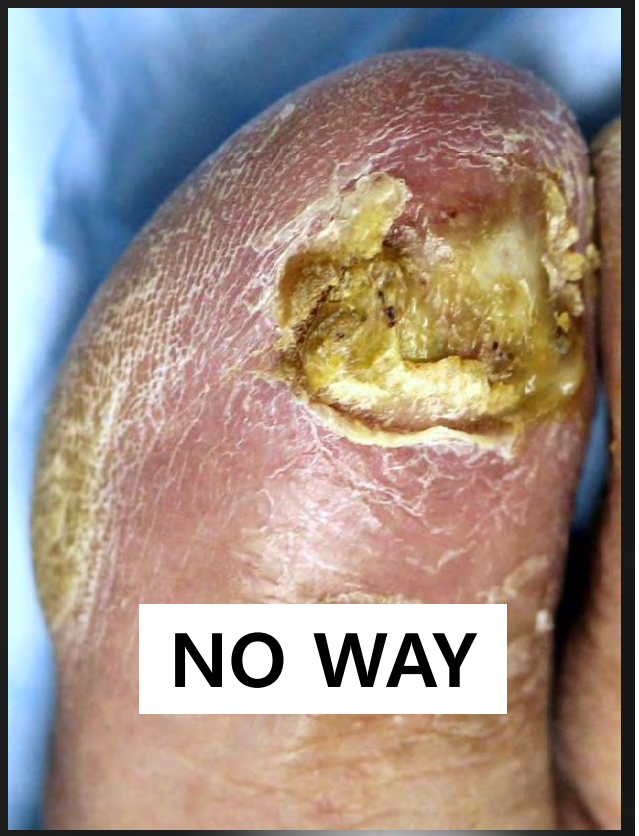
Oncyhomycosis: Expanded Rx Options

- **Understand the limitation of new agents**
- **Pivotal studies done w/ QD application for 48 weeks: Need dedicated patient**
- **Nails were 20-50-60% involved**
- **Involvement did not extend to matrix**
- **Subungual debris modest at initiation**

Topical Therapy?







Treat Onychomycosis Early

JANUARY 2015 58 VOLUME 14 • ISSUE 1

ORIGINAL ARTICLES JOURNAL OF DRUGS IN DERMATOLOGY

Efinaconazole Topical Solution, 10%: The Benefits of Treating Onychomycosis Early

Phoebe Rich MD
Oregon Dermatology and Research Center, Portland, OR

ABSTRACT

Objective: To evaluate efficacy of efinaconazole topical solution, 10% in onychomycosis patients with early and long-standing disease.
Methods: An analysis of 1655 patients, aged 18-70 years, randomized to receive efinaconazole topical solution, 10% or vehicle from two identical multicenter, double-blind, vehicle-controlled 48-week studies evaluating safety and efficacy. The primary end point was complete cure rate (0% clinical involvement of target toenail, and both negative potassium hydroxide examination and fungal culture) at Week 52. Three groups were compared: those with early disease (<1year), patients with a baseline disease of 1-5 years, and those with long-standing onychomycosis (>5years).
Results: The majority of patients had long-standing disease; were older, male and white. While nail involvement of the target toenail did not differ noticeably amongst the three groups, the number of nails involved did increase progressively with disease duration. Differences were seen in terms of infecting pathogens in early disease that might have important treatment implications. Efinaconazole was more effective in treating early disease, however more than 40% of patients with long-standing disease were considered treatment successes.
Limitations: A period of 52 weeks may be too brief to evaluate a clinical cure in onychomycosis.
Conclusions: Treatment of onychomycosis early to avoid disease progression to other toenails is important. Once daily efinaconazole topical solution, 10% is particularly effective in these patients.

J Drugs Dermatol. 2015;14:58-62

Treat Concomitant Tinea Pedis

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Management of Onychomycosis and Co-Existing Tinea Pedis

Shari R. Lipner MD PhD and Richard K. Scher MD FACP

Weill Cornell Medical College, New York, NY

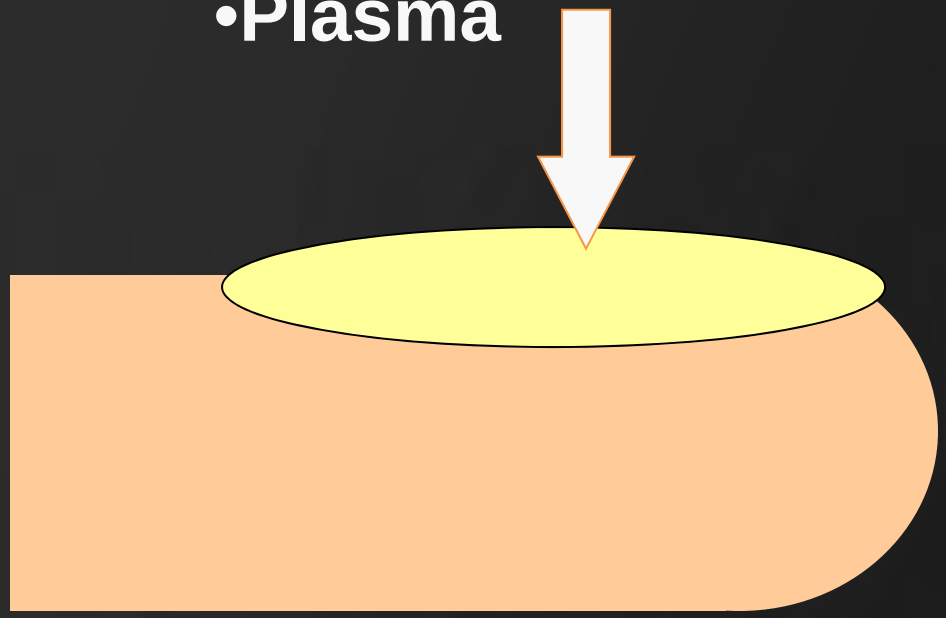
ABSTRACT

Onychomycosis is a common nail infection that often co-exists with tinea pedis. Surveys have suggested the diseases co-exist in at least one third of patients, although actual numbers may be a lot higher due to significant under-reporting. The importance of evaluating and treating both diseases is being increasingly recognized, however, data on improved outcomes, and the potential to minimize re-infection are limited. We review a recent post hoc analysis of two large studies treating mild to moderate onychomycosis with efinaconazole topical solution, 10%, demonstrating that complete cure rates of onychomycosis are significantly improved when any co-existing tinea pedis is also treated.

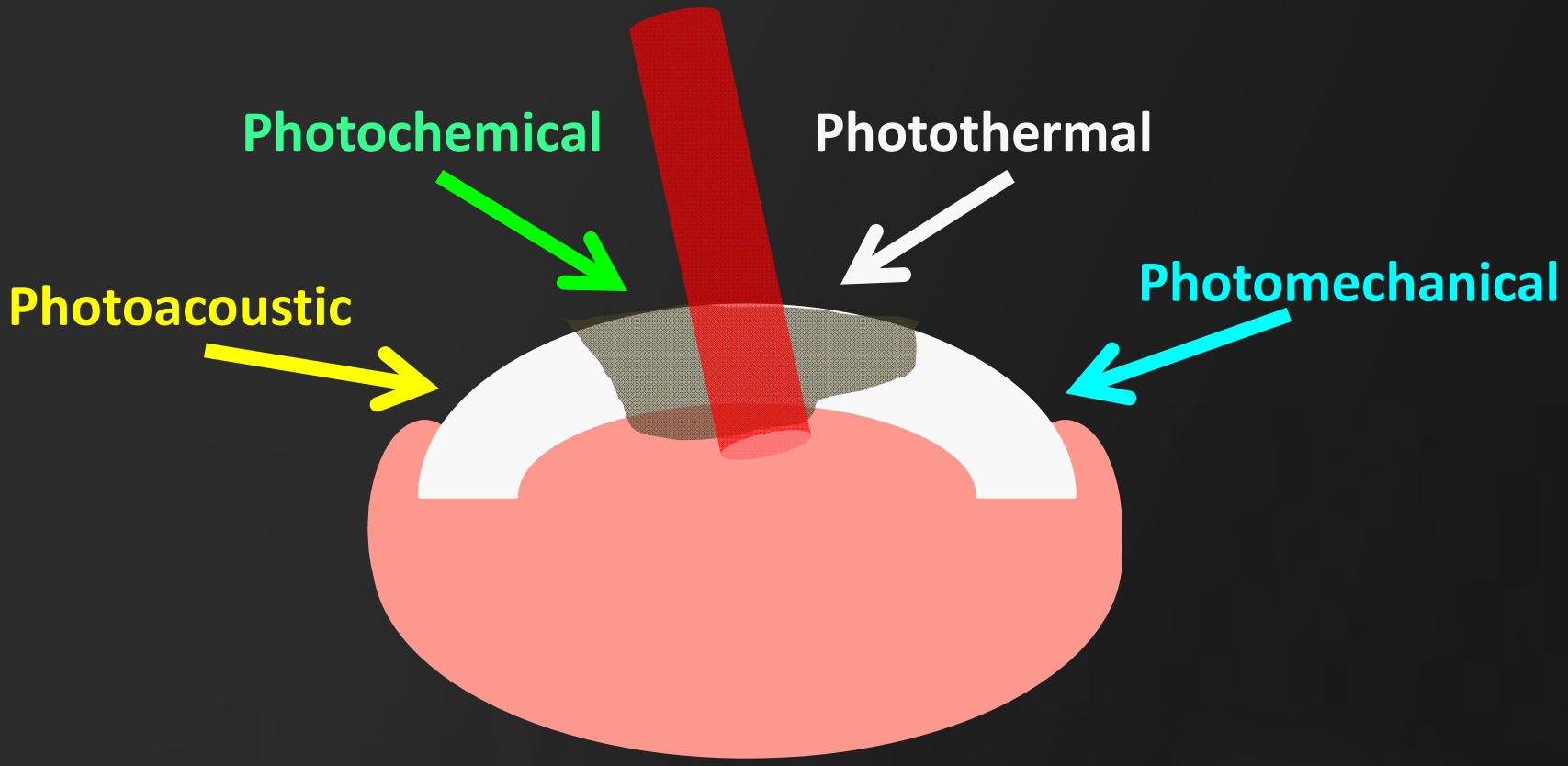
J Drugs Dermatol. 2015;14(5):492-494.

Device Therapy

- Lasers
- PDT
- Nail Drilling
- Plasma



How Do Lasers Work?



The anti-targeting of healthy tissue is as important as targeting fungi

What About LASER Therapy?

J. Fungi **2015**, *1*, 44-54; doi:10.3390/jof1010044

OPEN ACCESS

Journal of Fungi

ISSN 2309-608X

www.mdpi.com/journal/jof

Review

Laser Therapy for Onychomycosis: Fact or Fiction?

Lucette Teel Liddell † and Ted Rosen †,*

Baylor College of Medicine, Department of Dermatology, 1977 Butler Blvd, Suite E6.200, Houston, TX 77030, USA; E-Mail: Lucette.Liddell@bcm.edu

† These authors contributed equally to this work.

* Author to whom correspondence should be addressed; E-Mail: rosen@bcm.edu; Tel.: +1-713-794-7129; Fax: +1-713-794-7863.

Academic Editor: David Perlin

Received: 12 January 2015 / Accepted: 24 March 2015 / Published: 3 April 2015

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† These authors contributed equally to this work.

* Author to whom correspondence should be addressed; E-Mail: rosen@bcm.edu; Tel.: +1-713-794-7129; Fax: +1-713-794-7863.

Academic Editor: David Perlin

Received: 12 January 2015 / Accepted: 24 March 2015 / Published: 3 April 2015

Clear Nail: Now What?

Throw away shoes? Or…sanitize them (ozone, UVC)
Change socks; Wash dirty ones at 60^0C for 45 minutes
Medicated powder in shoes, socks
Never go barefoot in hotel rooms, locker rooms, etc

J Dermatolog Treat 2014;25:251-5
J Cutan Med Surg 2013;17:243-9

J Am Pod Med Assoc 2012:102;309-313

Oral ketoconazole should not be used as first-line therapy for ANY fungal infection

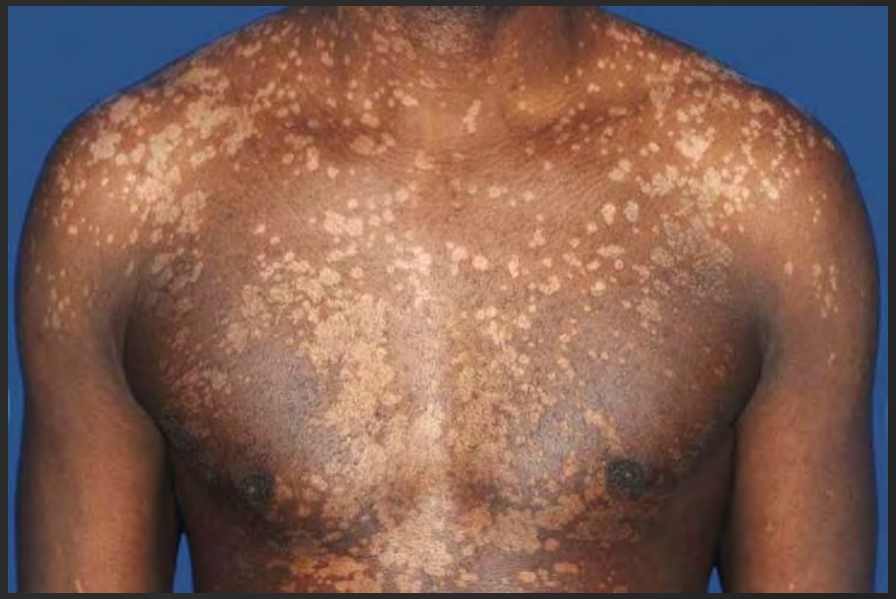
Ketoconazole should be used only for treatment of life-threatening mycoses when the potential benefits outweigh the risks and alternative therapeutic options are not available or not tolerated

Oral ketoconazole is no longer indicated for dermatophyte or Candida infections

Oral ketoconazole is not indicated for fungal infections of the skin or nails

Contraindicated in any individual with liver disease

Tinea Versicolor



- **Alternative orals (off label)**
- **Itraconazole 400mg/d x 3d or 200mg/d x 5d**
  J Dermatolog Treat 2002;13:185-7
- **Fluconazole 300mg QWk x 2**
  Mycoses 2007;50:311-13

CAUTION: Fluconazole & Pregnancy

JAMA The Journal of the American Medical Association

OR ~1.5

Original Investigation | January 5, 2016

Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth

Ditte Mølgaard-Nielsen, MSc[1]; Henrik Svanström, PhD[1]; Mads Melbye, MD, DrMedSci[1]; Anders Hviid, MSc, DrMedSci[1]; Björn Pasternak, MD, PhD[1]

[+] Author Affiliations

JAMA. 2016;315:58-67

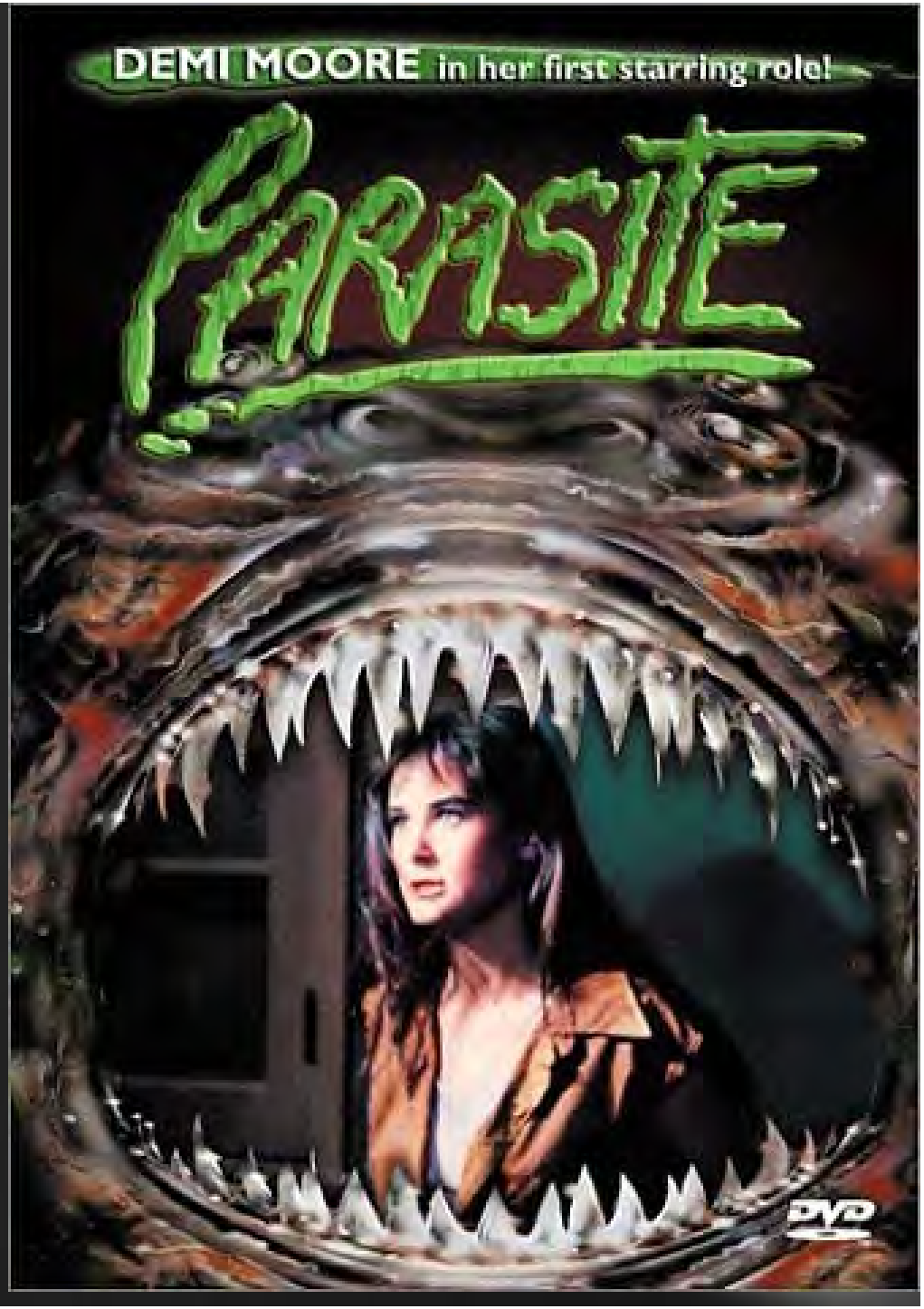
New Antifungal Drug!

- Isavuconazonium sulfate
- Becomes isavuconazole
- Oral and IV new azole antifungal
- Loading: 372mg Q8h x 6 doses, then 372mg QD
- Approved for aspergillosis and mucomycosis
- Nausea, vomiting, diarrhea (>20%); Headache, ↑LFTs hypokalemia, constipation, dyspnea, peripheral edema (10-15%)
- Infusion reactions and severe allergic and skin reactions (EM-SJS)

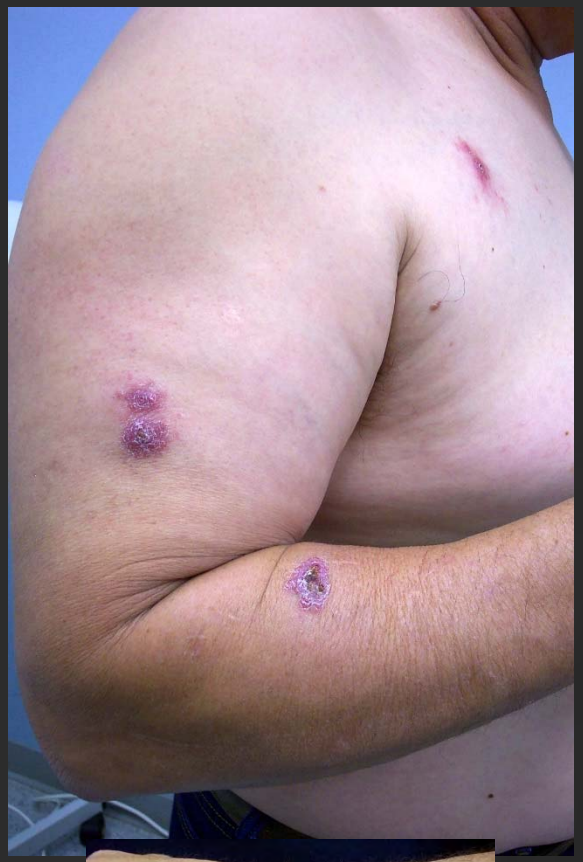
Expert Rev Anti Infect Ther. 2015;13:9-27

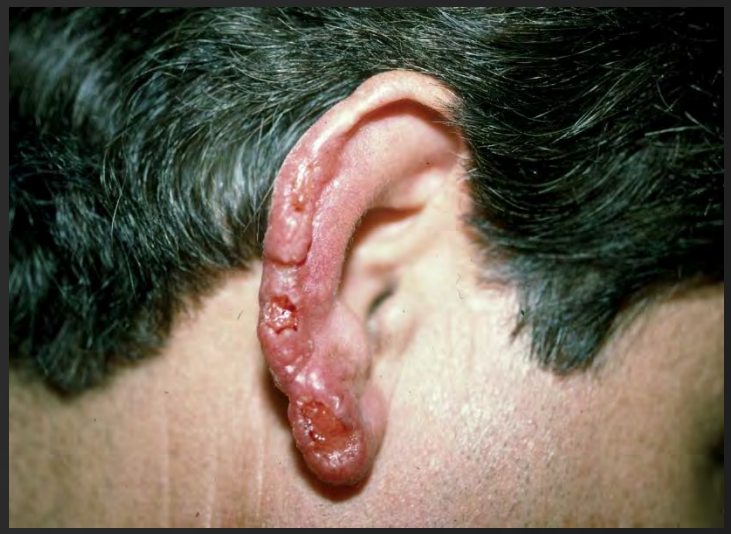
Mucormycosis

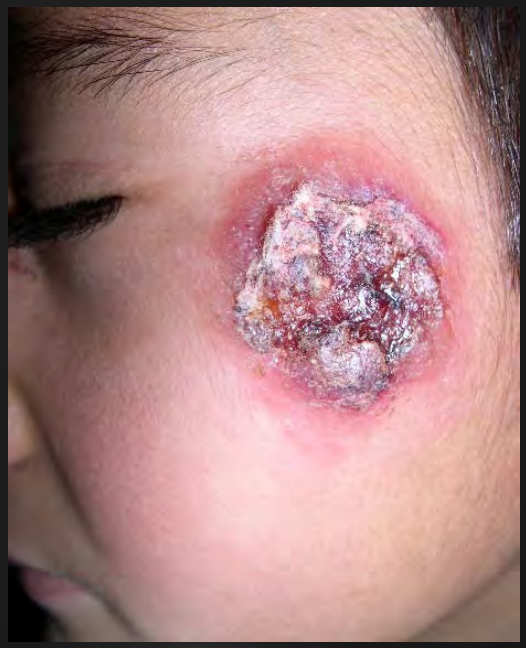
PARASITES

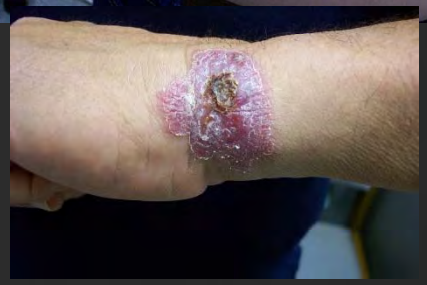


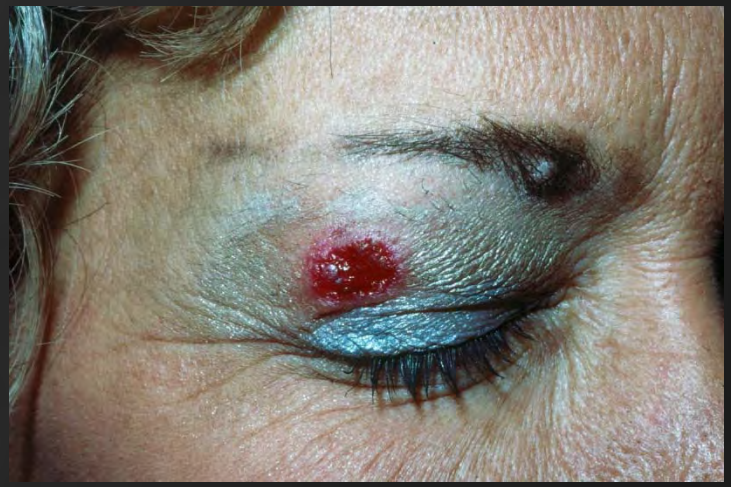
What do these four people share?











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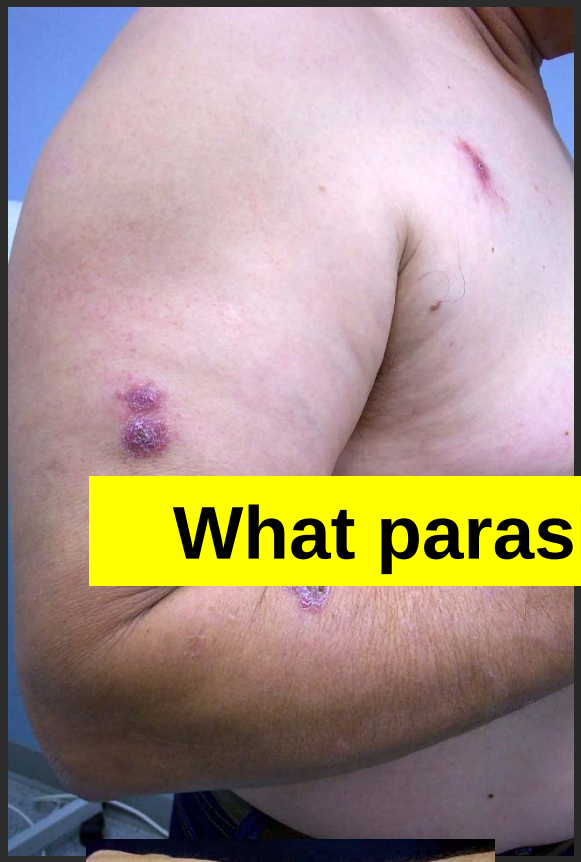
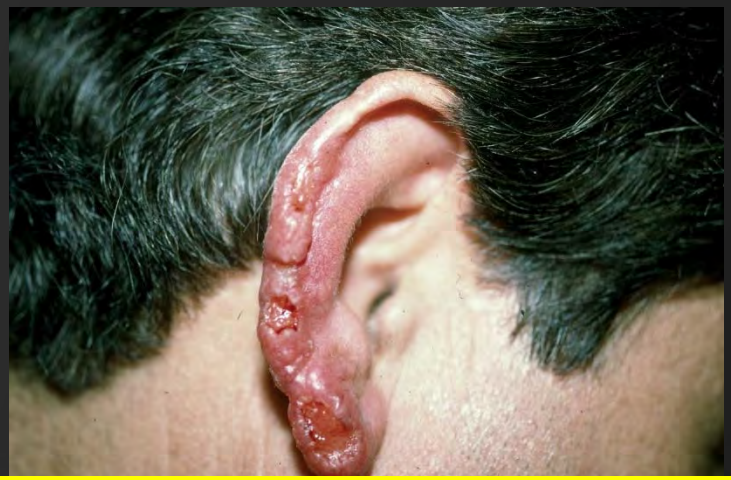
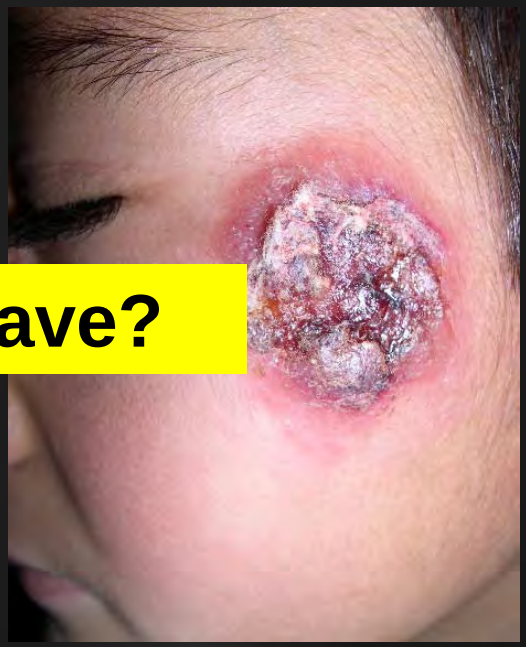
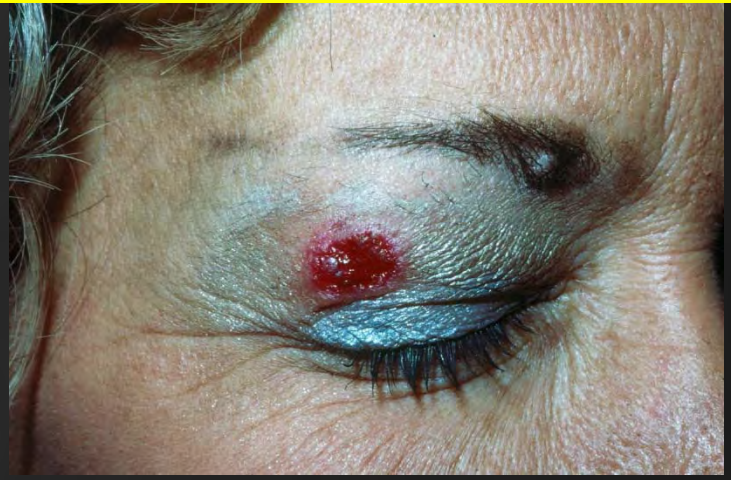
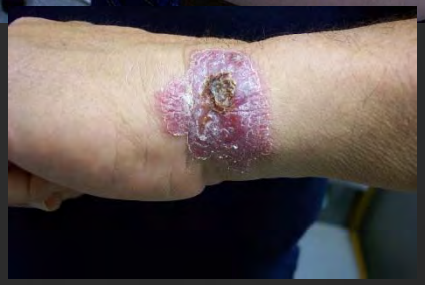






What parasitic disease do they have?





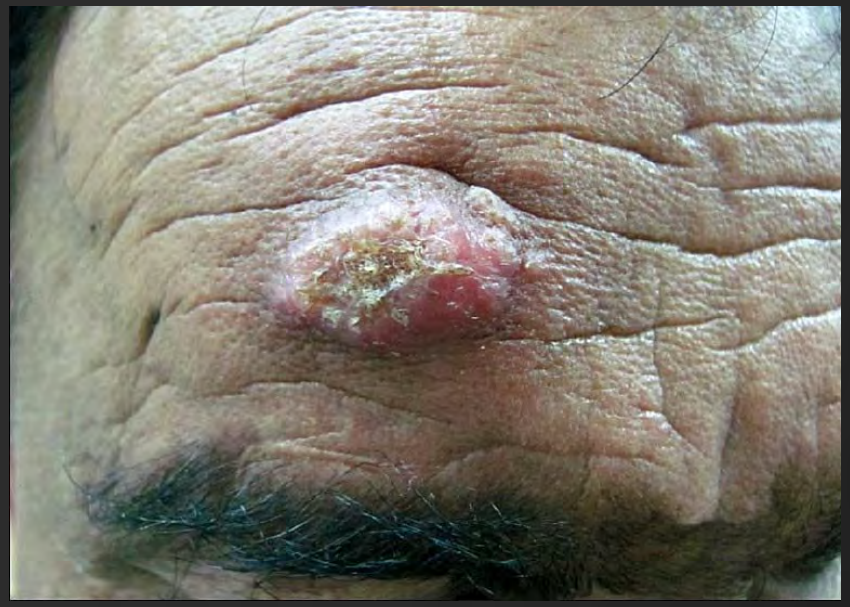
New Leishmaniasis Drug

- **Miltefosine** (hexadecylphosphocholine, a lecithin derivative)
- **Supplied as 50mg capsule**
- **Interferes w/ parasite membrane protein kinase (signaling)**
- **Approved 3-19-14: cutaneous, mucosal, visceral dz**
- **Good for most:** ***L. panamensis, guyanensis, braziliensis***
- **Less (but still positive) evidence benefit for** ***L. major, tropica***
- **Dose = 100-150mg po daily x 28d** ***(higher dose ≥ 45kg)***
- **AEs: anorexia, nausea, vomiting, diarrhea, H/A, mild ↑ LFTs, mild ↑Cr, and mild thrombocytopenia**
- **Pregnancy category X (contraindicated): Do not take if pregnant, use adequate contraception during Rx and for five months after therapy has been discontinued** ***(Black box)***

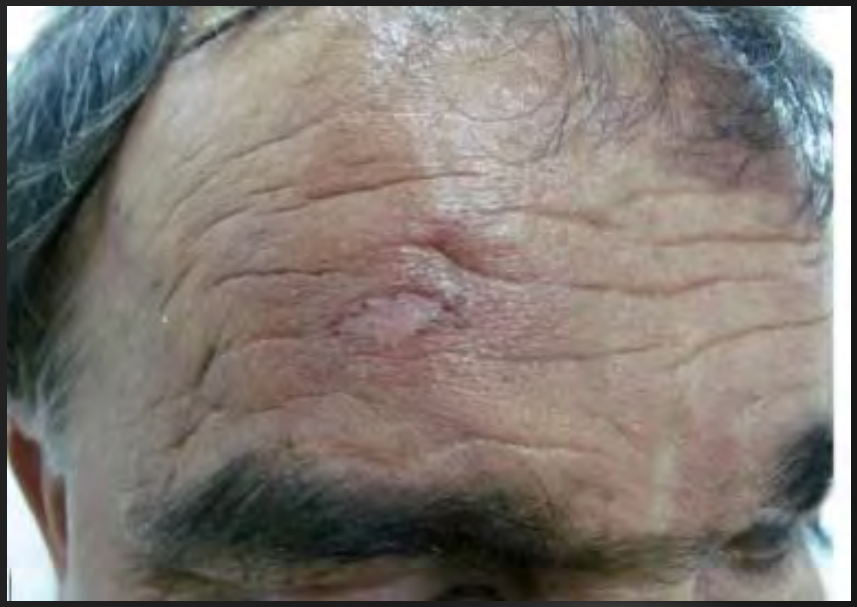
Med Lett Drugs Ther. 2014;56:89-90

New Leishmaniasis Drug

PRE-Rx



POST-Rx



PEDICULOSIS CAPITIS

Head Louse Treatments

PRODUCT	AGE (Lowest)	APPLICATIONS	COST (AWP) 4oz
Ivermectin Lotion 0.5%	6 MONTHS	ONE	$260
Spinosad 0.9% Suspension	6 MONTHS	TWO (7 days)	$219
Benzyl Alcohol 5% Lotion	6 MONTHS	TWO (7 days)	$53
Pyrethrin Shampoo	2 YEARS	TWO (7-10 days)	$50-80
Permethrin 1% Crème Rinse	2 MONTHS	TWO (7 days)	$80
Malathion 0.5% Lotion	6 YEARS	TWO (7-9 days)	$300

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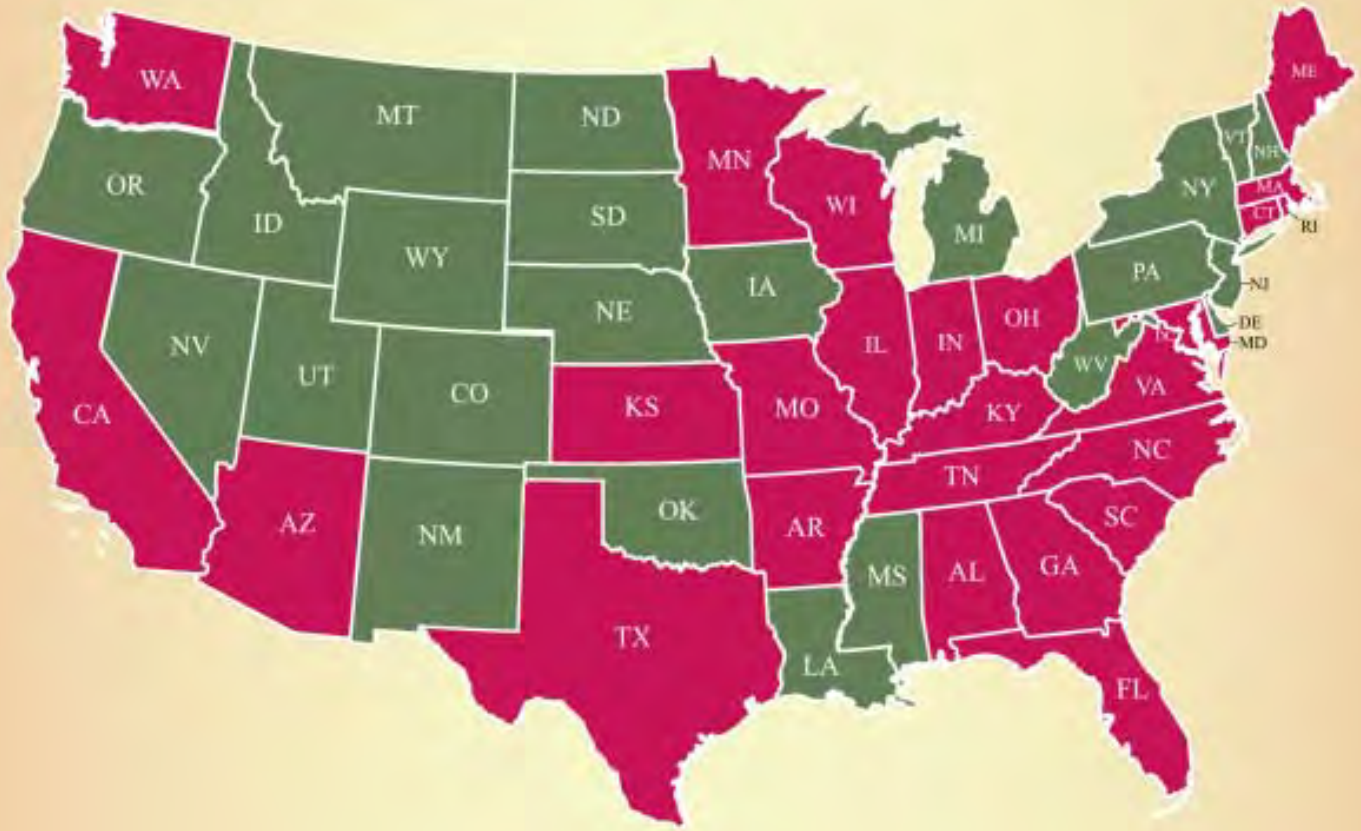
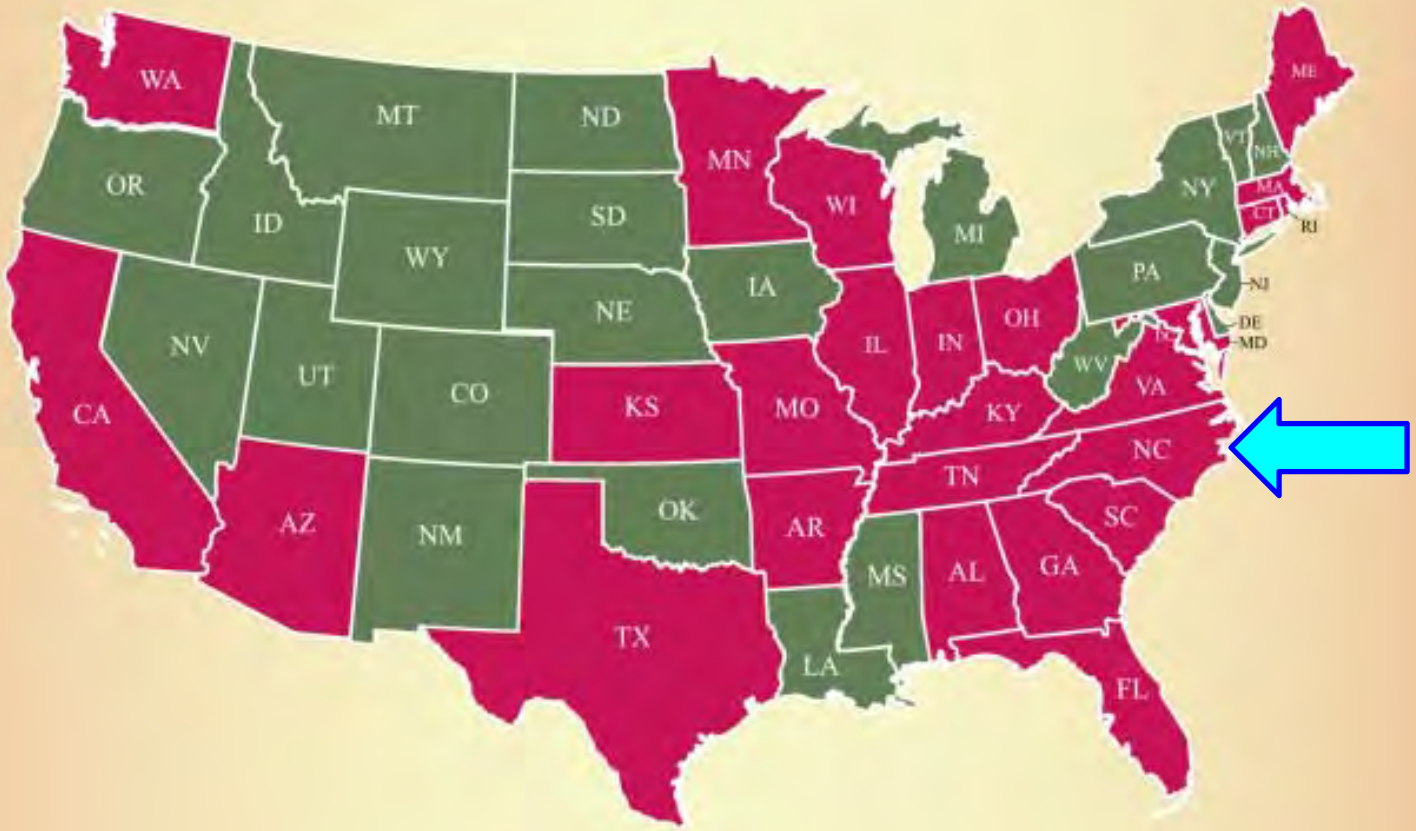
RESISTANCE IS REAL

Super Lice: Resistant!



J Med Entomol. 2014;51:450-7

Super Lice: Resistant!



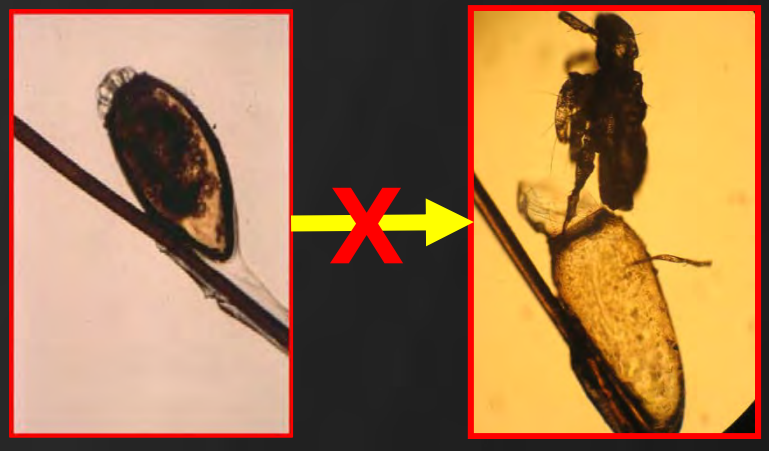
J Med Entomol. 2014;51:450-7

Head Lice in Young Adults!!!!!

Selfie Craze!

Abametapir = Xeglyze

- Abametapir 0.74%
- Blocks metalloproteinases
- Prevents egg from opening (no nymphs)
- Interferes w/ vital enzymes in adults
- Ovicidal and Pediculocidal
- Single 10 minute application



Abametapir = Xeglyze

- Phase 3, 14 sites USA with 704 patient
- Day 1: 90%
- Day 7: 88.5%
- Day 14: 81-82%
- No nit combing required
- No known resistance

NCT02062060
NCT02060903

Bedbugs

2015 Top Bedbug Cities; Orkin Jan 16, 2016

(with movement from 2014)

1. Chicago
2. Los Angeles (+2)
3. Washington DC (+11)
4. New York (+14)
5. Columbus, Ohio (-2)
6. Philadelphia
7. Detroit (-5)
8. Cincinnati (-1)
9. Richmond, VA
10. Baltimore (+21)
11. Raleigh-Durham,NC (+6)
12. Cleveland (-7)
13. Dallas-Ft. Worth (-7)
14. San Francisco (+2)
15. Indianapolis (-4)
16. Charlotte, NC (+14)
17. Houston (-5)
18. Denver (-10)
19. Atlanta (+6)
20. Buffalo, NY(+6)

2015 Top Bedbug Cities; Orkin Jan 16, 2016

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18. Denver (-10)
19. Atlanta (+6)
20. Buffalo, NY(+6)

Resistant Bedbugs!

- Genetic mutations:
- Thicker cuticle (skin)
  - ↓ Penetration insecticides
- Upregulated CYP450
  - ↑ Metabolic degradation
- Stabilized neurons
  - ↓ Tetanic firing of neurons

Pest Manag Sci. 2015;71:914-22
Sci Rep. 2013;3:1456
Arch Insect Biochem Physiol. 2010;73:245-57

Emerging Infections

ARBOVIRUS


JAMIE LEE CURTIS
WILLIAM BALDWIN
DONALD SUTHERLAND
VIRUS
Earth is in for a shock.
NOW AVAILABLE ON VIDEOCASSETTE AND DVD!

Dengue Vaccine!

- First Dengue vaccine
- CYD-TDV (Sanofi)
- Approved in Mexico, Brazil, Philippines
- 60% effective overall
- NOT very good vrs Serotype 2

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HEALTH

First Dengue Fever Vaccine Gets Green Light in 3 Countries

The mosquito-borne disease afflicts millions, and has had no approved vaccine until now

By Dina Fine Maron on December 30, 2015 Véalo en español

Sci Am Dec 30, 2015
N Engl J Med. 2015;373:1195-206

BETTER Dengue Vaccine

- **TV003/TV005 Developed by NIAID, NIH**
- **Live, attenuated tetravalent virus**
- **In small Phase 2 studies, 100% protective against all four types of Dengue**

Expert Rev Vaccines. 2016;15(4):509-17
Sci Transl Med. 2016 Mar 16;8(330):330ra36
JAMA. 2016 May 3;315(17):1825

Zika!!

- Arbovirus
- Transmitted by Aedes genus of mosquitoes
- 80% Asymptomatic
- Fever, H/A, myalgia, arthralgia, conjunctivitis
- Maculopapular rash
- Associated with microcephaly, Guillain-Barre
- Sexual transmission (M->F, M->M) documented
  - Virus persists in semen longer than blood
  - Condom use if male lived in / traveled to endemic area and has pregnant partner
- *No vaccine, No specific therapy*

MMWR. February 5, 2016 / 65(5);1–2
Emerg Infect Dis. 2015;21:1887

J Med Entomol. 2016;53:480-3

Journal of Medical Entomology, 2015, 1–4
doi: 10.1093/jme/tjv200
Short Communication

OXFORD

Short Communication

Clip-on Repellent Device With Metofluthrin Tested on *Aedes aegypti* (Diptera: Culicidae) for Mortality at Different Time Intervals and Distances

Christopher S. Bibbs[1] and Rui-De Xue

Anastasia Mosquito Control District, 500 Old Beach Rd., St. Augustine, FL 32080 (csbibbs@outlook.com; xueamcd@gmail.com), and [1]Corresponding author, e-mail: csbibbs@outlook.com

This is a research report only and mention of specific names of commercial products does not imply endorsement by the Anastasia Mosquito Control District.

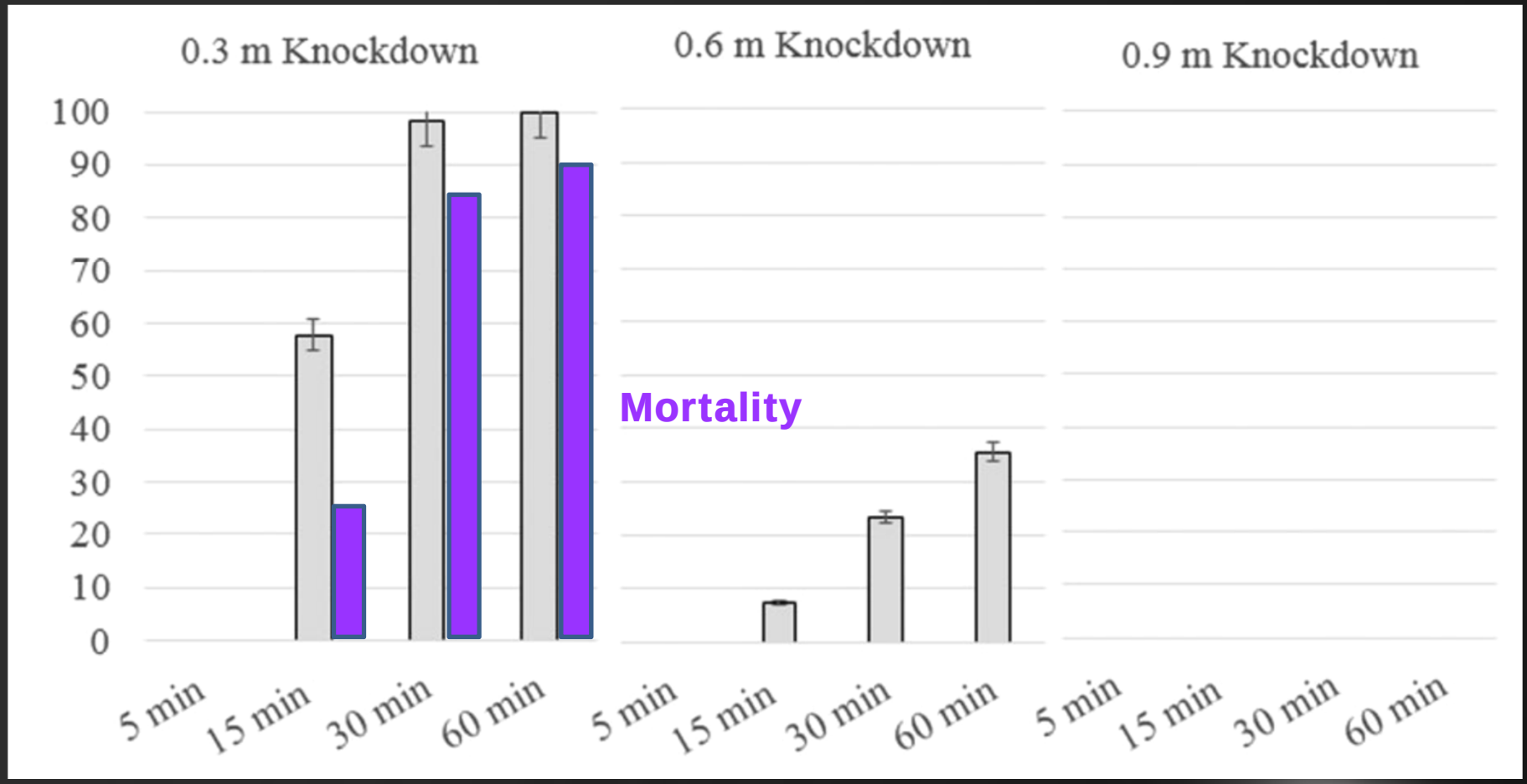
Received 19 June 2015; Accepted 24 November 2015

Abstract

The OFF! Clip-on mosquito-repellent device was tested outdoors against *Aedes aegypti* (L.). A single treatment device was used against batches of caged adult, nonblood fed *Ae. aegypti* at multiple locations 0.3 m from treatment center. Another set of cages was stationed 0.6 m from treatment. A final set of cages was placed 0.9 m away. Trials ran for durations of 5, 15, 30, and 60 min. Initial knockdown and mortality after 24 h was recorded. The devices had effective knockdown and mortality. This was not sustained at distances greater than 0.3 m from the device.

Zika: Mosquito Repellent

Clip-on Device with Metofluthrin



J Med Entomol. 2016;53:480-3

No Specific Anti-viral Therapy, So…

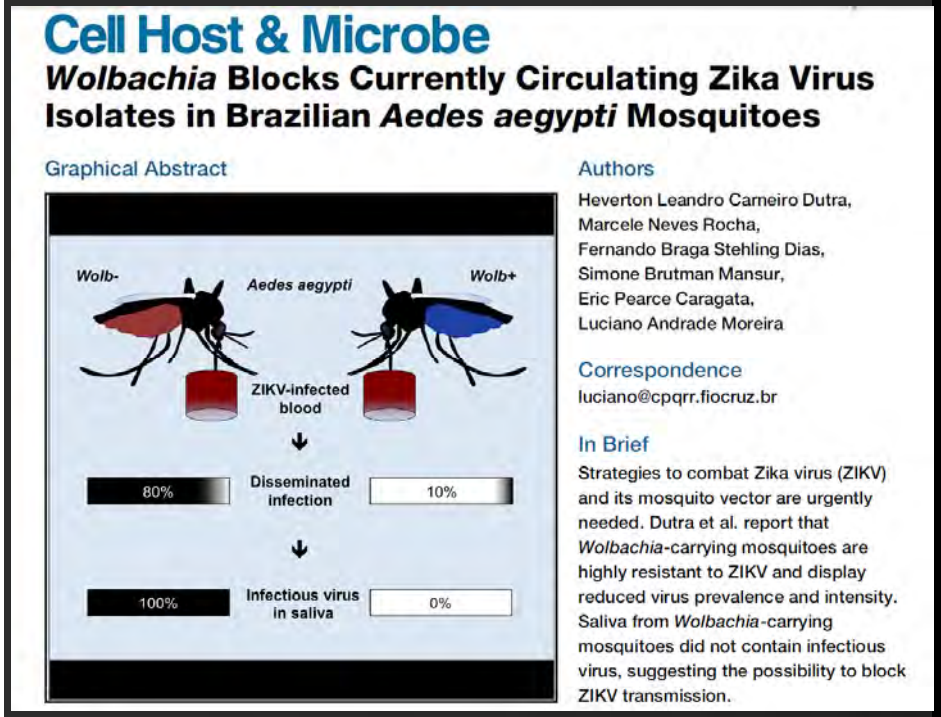
AP / *January 25, 2015, 2:32 PM*

FDA debates releasing genetically modified mosquitoes into Florida Keys

This undated photo made available by Oxitec shows a genetically modified Aedes aegypti mosquito in their U.K. lab. / **AP PHOTO/OXITEC, DERRIC NIMMO**

- **Oxitec (offshoot of Oxford Univ, UK)**
- **MALE Aedes aegypti mosquitoes**
- **Contains proteins from HSV and E. coli bacteria and genes from coral and cabbage**
- **Offspring (larvae) die before flying or biting**
- **Males feed on nectar, not on blood so should not introduce modified DNA into human**
- **Recent tests in Cayman Islands and Brazil killed >96% of newly hatched insects**

No Specific Anti-viral Therapy, So…



Cell Host & Microbe

Wolbachia Blocks Currently Circulating Zika Virus Isolates in Brazilian *Aedes aegypti* Mosquitoes

Graphical Abstract

Authors

Heverton Leandro Carneiro Dutra,
Marcele Neves Rocha,
Fernando Braga Stehling Dias,
Simone Brutman Mansur,
Eric Pearce Caragata,
Luciano Andrade Moreira

Correspondence

luciano@cpqrr.fiocruz.br

In Brief

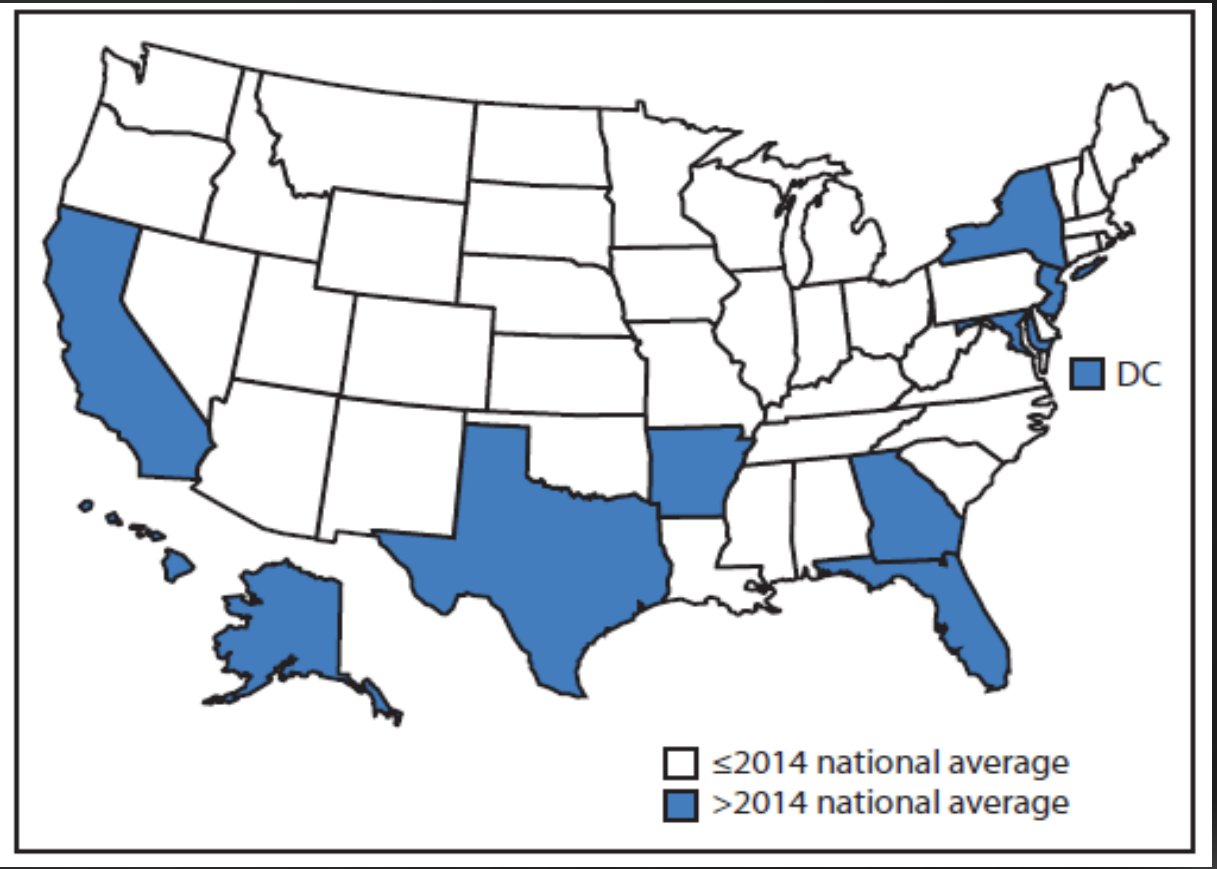
Strategies to combat Zika virus (ZIKV) and its mosquito vector are urgently needed. Dutra et al. report that *Wolbachia*-carrying mosquitoes are highly resistant to ZIKV and display reduced virus prevalence and intensity. Saliva from *Wolbachia*-carrying mosquitoes did not contain infectious virus, suggesting the possibility to block ZIKV transmission.

Cell Host & Microbe 2016;19:1–4.

- **Monash University, Australia Brazilian Ministry of Health**
- **Aedes aegypti mosquitoes prior infected with Wolbachia bacteria**
- **Fed human blood infected with Zika virus of two strains**
- **The mosquitoes with bacterial infection developed disseminated viral infection 80% less frequently AND….**
- **Virus in saliva of such mosquitoes was non viable**

The Future

TB: USA, 2014

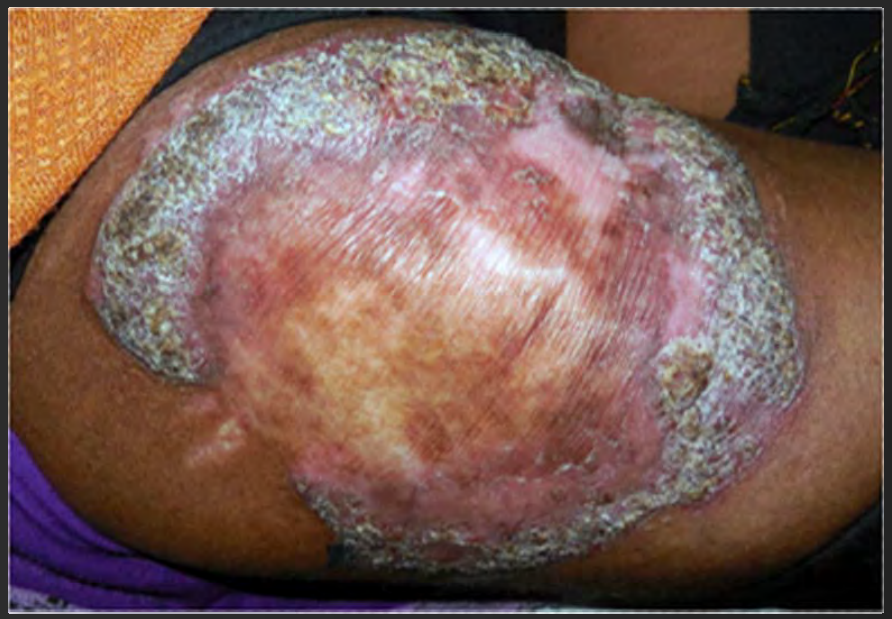


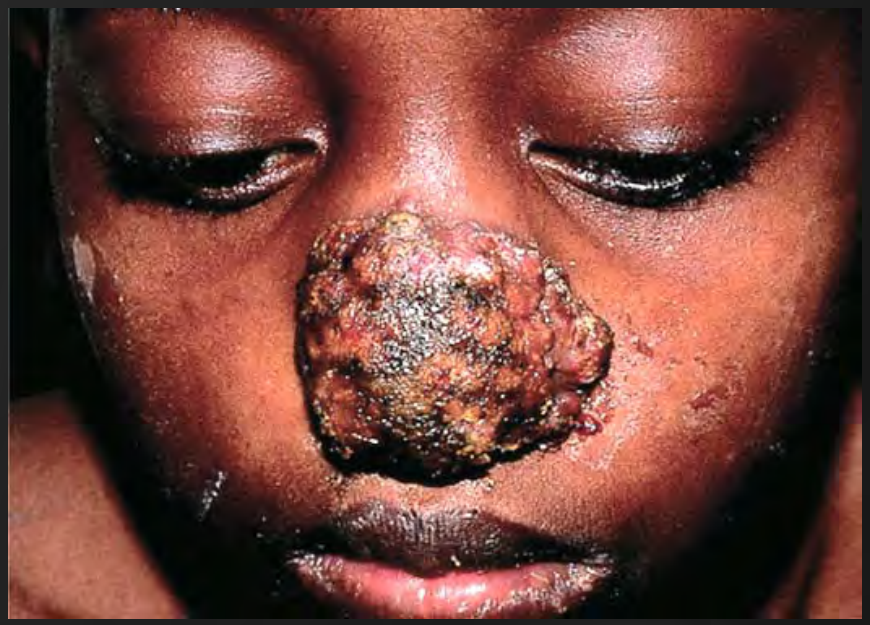
MMWR 2015;65:265-69

Tuberculosis

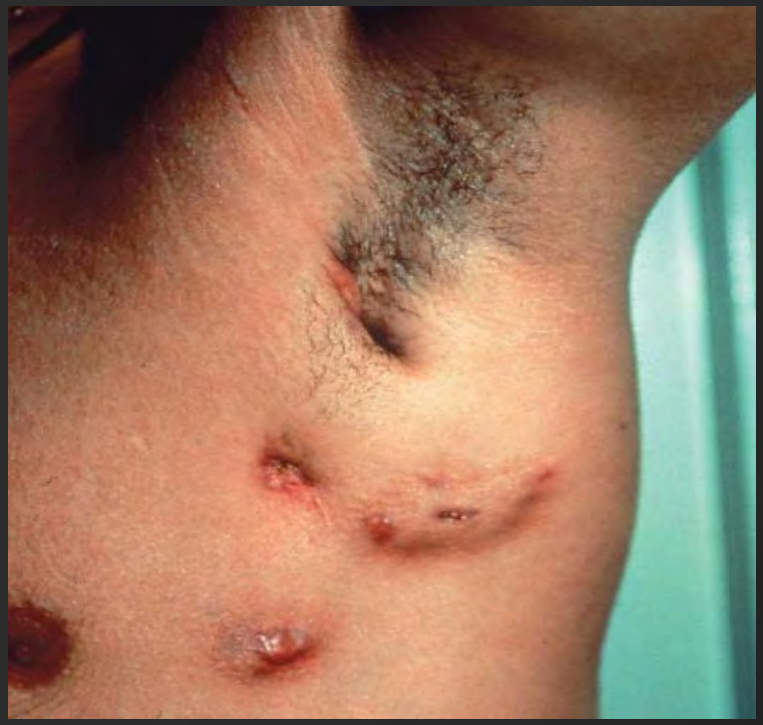
- Pulmonary
- Pericarditis
- CNS: meningitis
- Lymphatic: scrofula
- Bones, Joints and Spine
- Gastrointestinal: enteritis, hepatobiliary, pancreatitis
- Ocular
- TB of the middle ear
- Nephritis
- Cutaneous

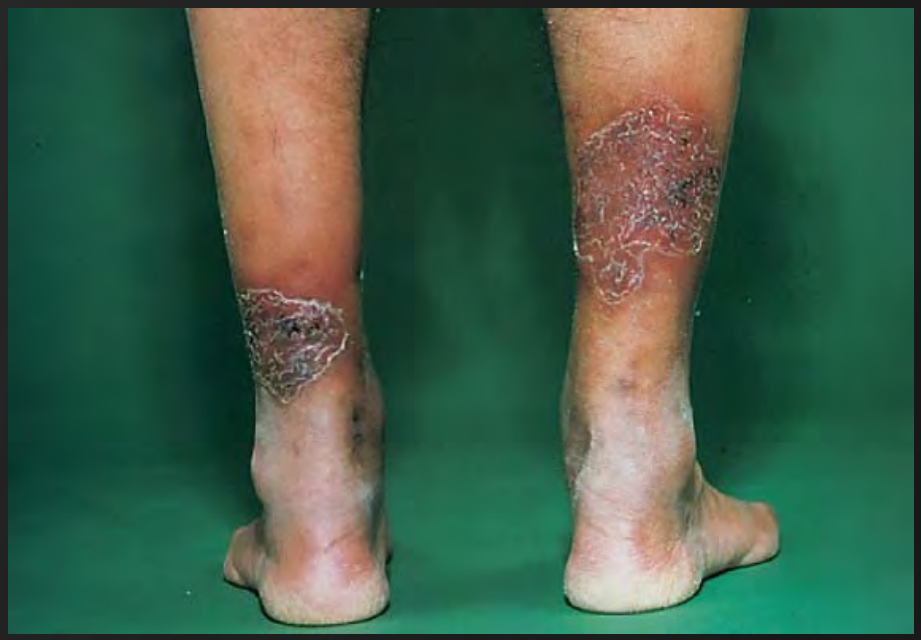
Cutaneous Tuberculosis





Cutaneous Tuberculosis





TB Vaccines

Prophylactic Vaccines

Phase	Tb vaccine	Tb vaccine type	Sponsorship
Phase I	AdAg85A	Viral vectored	McMaster CanSino
	MTBVAC	Attenuated *Mycobacterium tuberculosis* strain	TBVI, Zaragoza, Biofabri
	ID93+GLA-SE	Protein/adjuvant	Infectious Disease Research Institute (IDRI), Aeras
	Crucell Ad35/MVA85A	Viral vectored	Crucell, Oxford, Aeras
	DAR 901	Mycobacterial – whole cell or extract	Darmouth, Aeras
	TB/FLU-04L	Viral vectored	Research Institute for Biological Safety Problems, Research Institute of Influenza
Phase II	VPM 1002	rBCG	Max Plank, VPM, TBI, Serum Institute
	H1+IC31	Protein/adjuvant	SSI, TBVI, EDCTP, Intercell
	RUTI	Mycobacterial, whole cell or extract	Archivesl Farma, S.I.
	H56:IC31	Protein/adjuvant	SSI, Aeras, Intercell
	H4:IC31	Protein/adjuvant	SSI, Sanofi-Pasteur, Aeras, Intercell
	Crucell Ad35/ AERAS-402	Viral vectored	Crucell, Aeras
Phase IIb	MVA85A	Viral vectored	Oxford, Aeras
	M72+AS01$_E$	Protein/adjuvant	GSK, Aeras
Phase III	*M. Vaccae*	Mycobacterial, whole cell or extract	Anhui Zhifei Longcom

rBCG, recombinant Bacille Calmette Guerin.

Therapeutic Vaccines

Tb vaccine	Immune response	References
AdAg85A	IFN-γ	De Val *et al.* [2012]
	CD4$^+$ and CD8$^+$ T cells	Santosuosso *et al.* [2005]
ID93+GLA-SE	T_H1 (IFN-γ, TNF-α and IL-2) CD4$^+$ T cell (IFN-γ and TNF-α)	Orr *et al.* [2013, 2014]
Crucell Ad35/MVA85A	IFN-γ	Radosevic *et al.* [2007]; Magali *et al.* [2013, 2014]; Abel *et al.* [2010]
	CD4$^+$ T cell	Dintwe *et al.* [2013]; Satti *et al.* [2014]; Tameris *et al.* [2013]
DAR 901	IFN-γ	http://www.tbvaccines2013.org/wp
VPM 1002	CD4$^+$ and CD8$^+$ T cell	Grode *et al.* [2013]; http://www.vakzine-manager.de/en/resources/Produkte/VPM1002_en.pdf
H1+IC31	T_H1 (IFN-γ, IL-2)	Reither *et al.* [2014]
RUTI	T_H1 (IFN-γ), T_H2, T_H3 CD4$^+$ and CD8$^+$ T cells	Vilaplana *et al.* [2008]; Cardona and Amat [2006]; Guirado *et al.* [2008]
H56:IC31	CD4$^+$ T cell	Hoang *et al.* [2013]
H4:IC31	CD4$^+$ T cell (IFN-γ, TNF-α and IL-2)	Billeskov *et al.* [2012]
Crucell Ad35/AERAS-402	CD4$^+$ (IFN-γ, TNF-α and IL-2) and CD8$^+$ T cell (IFN-γ and TNF-α)	Abel *et al.* [2010]
MVA85A	IFN-γ	Minassian *et al.* [2011]; Magali *et al.* [2013, 2014]
	CD4$^+$ T cell	Satti *et al.* [2014]
	CD4$^+$ T cell (IFN-γ and IL-2)	Dintwe *et al.* [2013]
	CD4$^+$ T cell (IFN-γ, TNF-α, IL-2 and IL-17)	Scriba *et al.* [2010]
M72+AS01$_E$	CD4$^+$ T cell	Montoya *et al.* [2013]; Idoko *et al.* [2014]
	CD4$^+$ and CD8$^+$ T cell	Day *et al.* [2013]
Mycobacterium vaccae	IFN-γ and IL-10	Rodríguez-Güell *et al.* [2008]

IFN-γ, antigen-specific interferon γ; IL, interleukin; T_H1, T helper 1; TNF-α, tumour necrosis factor α.

Ther Adv Vaccines 2015;366-75.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Mushrooms: More than just hallucinogens

April 27, 2015

Shiitake Mushroom Intake Tied to Improved Human Immunity

Share this article:

Shiitake Mushroom Intake Tied to Improved Human Immunity

(HealthDay News) — Regular consumption of *Lentinula edodes* (shiitake) mushrooms is associated with improved human immunity, according to a study published online April 11 in the *Journal of the American College of Nutrition*.

Xiaoshuang Dai, from the University of Florida in Gainesville, and colleagues examined whether consumption of whole, dried shiitake mushrooms could improve human immune function in a study involving 52 healthy adults aged 21 to 41 years. Participants in the four-week, parallel-group study consumed 5 or 10 g mushrooms daily. Blood was drawn and saliva and serum were collected before and after the study.

The researchers observed increased ex vivo proliferation of γδ-T cells and natural killer T-cells (60 percent and two-fold increase, respectively; both $P < 0.0001$) with four weeks of mushroom consumption. A greater ability to express activation receptors was seen in both cell types with mushroom consumption. There was an increase in secretory immunoglobulin A in saliva and a reduction in C-reactive protein in serum. There was a significantly different pattern of cytokines secreted before and after mushroom consumption, with increased interleukin (IL)-4, IL-10, tumor necrosis factor α, and IL-1α levels, and decreased macrophage inflammatory protein-1α/chemokine C-C ligand 3 levels with consumption.

"Regular *L. edodes* consumption resulted in improved immunity, as seen by improved cell proliferation and activation and increased sIgA production," the authors write.

Funding was provided by the U.S. Mushroom Council and the Australian Mushroom Growers Association.

J Am Coll Nutr. 2015;34:478-87

Fungi as “Cultural Enhancers”!

- **Modern violin wood treated with fungi**
- ***Physisporinus vitreus***
  Xylaria longipes
- **Blind competition**
- **Audience preferred fungally treated over 1711 Stradivarius violin by 2:1 margin**
- **Produces wood w/ same properties as 18th century cold period**

CONCERTO FOR FUNGUS

How do you get to Carnegie Hall? Fungus might help.

Swiss researcher Francis W.M.R. Schwarze has found that applying two fungi, *Physisporinus vitreus* and *Xylaria longipes,* to the wood used in crafting a modern violin makes it sound like a Stradivarius, those rare, centuries-old instruments revered for their rich tone. In a blind competition in 2009, a knowledgeable audience preferred a violin made from fungally treated wood over a Stradivarius and untreated modern instruments. (In other blind tests, people often prefer modern instruments, and even legendary violinists have had trouble telling by sound which violin is which.) Dr. Schwarze and his colleagues are now trying to make 30 more violins with fungally treated wood.

Chem Eng News 90:80, 2012

Infection

- **“Infectious disease is one of the great tragedies of living things - the struggle for existence between two different forms of life... Incessantly, the pitiless war goes on, without quarter or armistice - a nationalism of species against species.”**
- **Hans Zinsser (1878-1940)**
- **Rats, Lice and History (1934)**

Thanks for your attention

Vitiligo Medical Update

North Carolina Dermatological Society
July 9, 2016

Seemal R. Desai, MD, FAAD
Clinical Assistant Professor
Department of Dermatology
University of Texas Southwestern Medical Center
Founder & Medical Director
Innovative Dermatology, PA
Dallas, Texas

Vitiligo

- **TREATMENT OPTIONS**
  - **Topicals including steroids, vit D analogues, calcineurin inhibitors**
  - **Depigmentation**
  - **Systemic tx**
  - **Phototherapy**
  - **Surgical Treatment**
  - **Psychological Therapy**
- **IF TREATMENTS FAIL → ANALYZE PATIENTS DESIRES**

Let's try to define!

- **Active/Unstable Vitiligo**
  - Depigmentation spreading more than 2% BSA in one month
- **Chronic Vitiligo**
  - Depigmentation present for at least 1 year with no h/o spontaneous repigmentation
- **Refractory Vitiligo**
  - Disease that is poorly responding to therapy→ <25% repigmentation

Stabilizing Vitiligo

- **Systemic Steroids**
  - **Oral Mini-Pulse Therapy (OMP)**
  - **Dexamethasone 4mg daily on 2 consecutive days per week**
    - **i.e Saturday and Sunday**
  - **Half the dose in children less than 16 years of age**
  - **Must counsel patients on side effects**

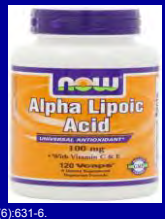
Parsad D, De D. Corticosteroid minipulses. In: Vitiligo. 1st ed. New York: Springer, 2010.p.319-24.
Pandya et al. DermQuest. *https://www.dermquest.com/expert-opinions/.../systemic-corticosteroids/*

Stabilizing Vitiligo

- **What I do**
  - **IM Triamcinolone Acetonide 60mg qmonth for 3 months**
  - **Transition to Oral Mini-Pulse Therapy (OMP), if still spreading**
    - **Dexamethasone 4mg daily on 2 consecutive days per week**
  - **Have the patient on a traditional therapy**
  - **Start patient on Calcium/Vitamin D supplement**

Antioxidants in Vitiligo

- **Number of studies support the use anti-oxidants**
- **Especially in combination with phototherapy (NBUVB)**
- **Alpha Lipoic Acid, Vit E, Vit C**



Dell'Anna ML et al. Clin Exp Dermatol. 2007 Nov;32(6):631-6.

Antioxidants in Vitiligo

- **28 Pts with non-segmental vitiligo**
  - **2 months before and for 6 months during the NB-UVB treatment**
  - **47% of pts > 75% repigmentation vs.18% in placebo group**
  - **Improvements in catalase activity, decrease in overall ROS production**
- *Oral antioxidants containing alpha-lipoic acid combined with NB-UVB enhanced repigmentation by reducing oxidative stress*

Picardo M *et al. Clin Exp Dermatol*, 2007 Nov;32(6):631-6

Antioxidants in Vitiligo

- ***Polypodium Leucotomas***
  - NBUVB 2x weekly
  - Treated with PLE 250mg TID vs placebo for 26 weeks
  - Higher repigmentation of head and neck region in test (44%) vs placebo group (27%) [*P* = 0.06]
    - Other sites with limited repigmentation

Middlekamp-Hup MA *et al. JEADV.* 2007;21:942-950

Antioxidants in Vitiligo

- 57 patients with generalized vitiligo
- Polypodium 480mg daily + NB-UVB vs. NB-UVB alone
- Response rate of the combined group significantly higher than the NB-UVB only group 40% vs. 22%, p<0.0005
- In responders, repigmentation was observed within the first month as compared to a mean of 3 mo in the group of phototherapy only patients

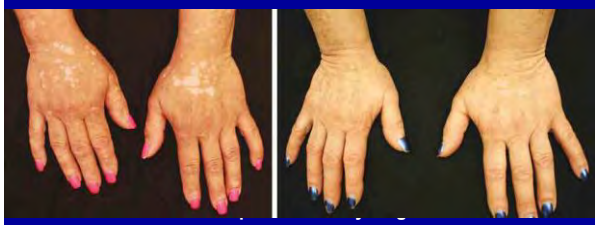
Pacifico, et al. Poster 3111. Paper presented at: Amer Acad of Dermatology; March 2009; San Francisco, CA.

Afamelanotide

- Analogue of α–melanocyte-stimulating hormone
- Binds with the melanocortin-1 receptor (MC1R)
  - MC1R is not expressed by melanocyte stem cells
  - Afamelanotide can stimulate pigmentation and increase proliferation of melanocytes
  - Phototherapy needed to induce melanoblast proliferation

Lim, H, JAMA Dermatol, 2015;151(1):42-50

Janus Kinase Inhibitors for Vitiligo

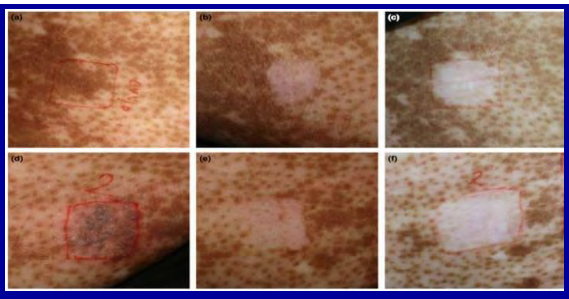


Craiglow BG et al. *JAMA Dermatol*, 2015;151(10):1110-1112

Tacrolimus in Vitiligo

- **Can use tacrolimus in combination with NBUVB**
- **Caution in pediatric population and long-term use**
- **Consider using 0.03% on face once daily and 0.1% on body**

Fai D1, Cassano N et al. JEADV. 2007 Aug;21(7):916-20.
Narrow-band UVB phototherapy combined with tacrolimus ointment in vitiligo: a review of 110 patients.



van Geel N, Depaepe L, Speeckaert R. Laser (755 nm) and cryotherapy as depigmentation treatments for vitiligo: a comparative study. J Eur Acad Dermatol Venereol. 2015 Jun; 29(6): 1121-1127.

Depigmentation in Vitiligo

- 20% Monobenzone topically
- I start with a small "zone"
  - i.e. one arm treated for 3-4 months
  - Stinging is usually NOT an allergic reaction
- Have the patient apply the cream BID for 3-4 days
- Female patients more likely to desire depigmentation
- Do NOT apply at night

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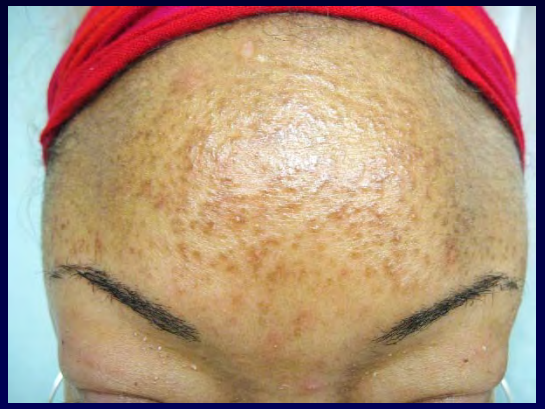
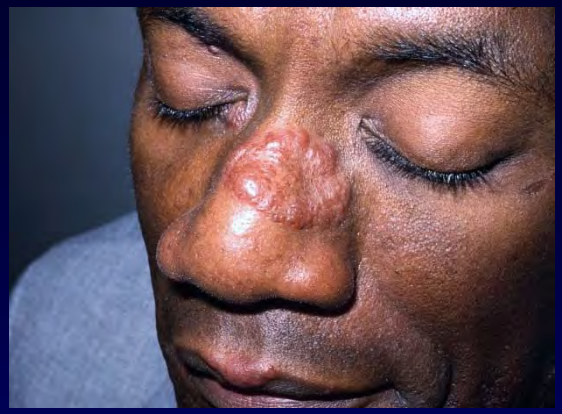
Depigmentation in Vitiligo

- Hair may or may not depigment, but eyes WILL NOT
- Recheck "zone" in person & via photos in 2-3 months
  - Pt usually pleased
- Can then treat other arm, face, neck
- ACD the most common side effect
- Some small "guttate" areas of repigmentation

Take Home Messages

- There are new therapies on the horizon!
- More randomized controlled trials are needed to evaluate the efficacy of up and coming treatments in the diagnosis, management and treatment of conditions such as vitiligo
- Have hope! Let's uplift, support and nurture each other to find a cure for this devastating disease which will NOT take us over!





Cutaneous Sarcoidosis 2016

Ted Rosen, MD

Baylor College of Medicine

Houston, Texas

Disclosures

- *NONE*
- *Neither I nor any member of my immediate family has a financial relationship or interest with any proprietary entity producing health care goods or services discussed in or related to the content of this CME talk*
- *The content of this talk will reference commercial products; however, I will use generic terms whenever possible and alternative therapies will be discussed*
- *I will discuss unapproved or investigative use of commercial products or devices, of necessity, due to a paucity of approved methods of treating the disease under discussion*

What Is Sarcoidosis?

?

Sarcoidosis

- *10-20x blacks*
- *15x death rate (b:w)*
- *Women > men (2:1)*
- *Peak age 20-40*
- *Rare under age 4*
- *Skin disease:*
  -implies chronicity
  -assoc w/ lung and bone involvement

- *Hilar adenopathy*
- *Lung infiltrate*
- *Uveitis*
- *Hepatomegaly*
- *Splenomegaly*
- *Conduction abn*
- *Osteolytic bone lesions; arthritis*
- *Fatal: 5-10%*

Med Clin North Am 99:1123-48, 2015

Sarcoid: Epidemiology, Updated

- *Retrospective study based on HMO data covering 5% of all lives in greater Detroit*[1]
- *African-American Women* *39.1/100,000*
- *African-American Men* *29.8/100,000*
- *Caucasian Women* *12.1/100,000*
- *Caucasian Men* *9.6/100,000*
- *Retrospective review of 12 year data from a single institution (Med Univ South Carolina)*[2]
- *Most common affected demographic: African-American Females*
- *Black compared to White: More organ systems involved and more often required intervention*

1. Am J Epidemiol 1997;145:234-41
2. Sarcoidosis Vasc Diffuse Lung Dis 2012;29:119-27

Prognosis *Med Clin North Am 99:1123-48, 2015*

Indicators of good clinical outcome

Löfgren syndrome

White

Young age

Bilateral hilar adenopathy

Indicators of poor clinical outcome

African American

Extrathoracic disease

Cutaneous manifestations, not including erythema nodosum

Neurologic and cardiac involvement

Older age

Parenchymal lung involvement

Prognosis *Med Clin North Am 99:1123-48, 2015*

Indicators of good clinical outcome

Löfgren syndrome **Hilar nodes, Arthralgia, Low grade Fever, Erythema nodosum**

White

Young age

Bilateral hilar adenopathy

Indicators of poor clinical outcome

African American

Extrathoracic disease

Cutaneous manifestations, not including erythema nodosum

Neurologic and cardiac involvement

Older age

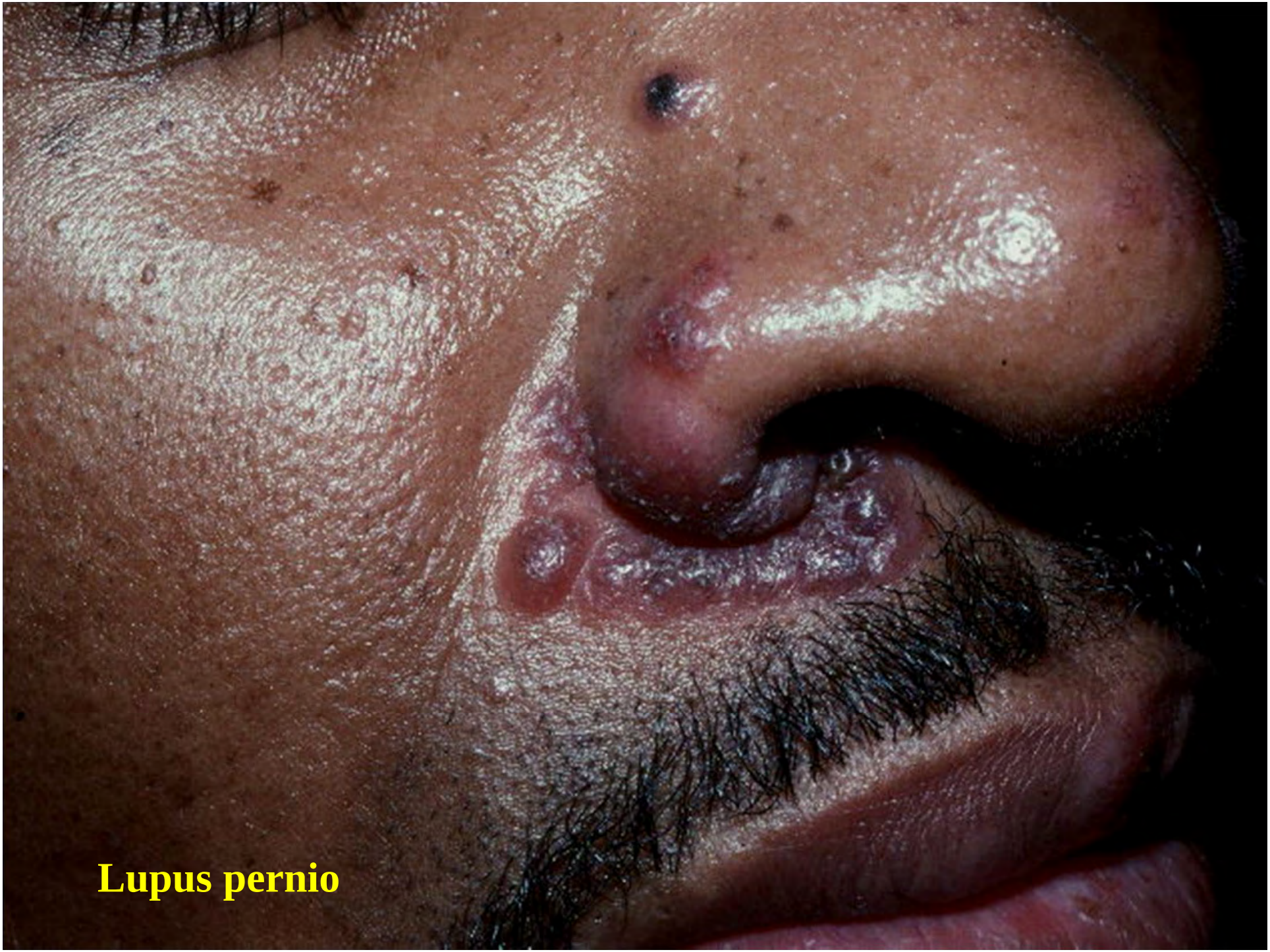
Parenchymal lung involvement

Sarcoid: Clinical Features

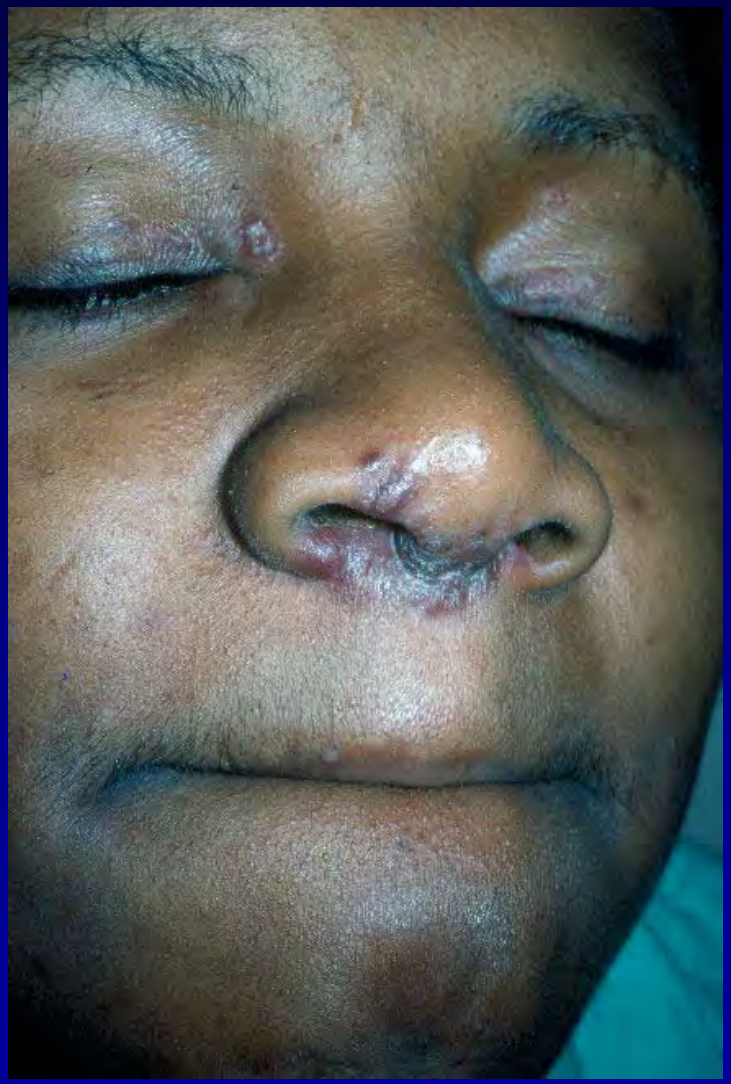
Sarcoidosis: Polymorphic

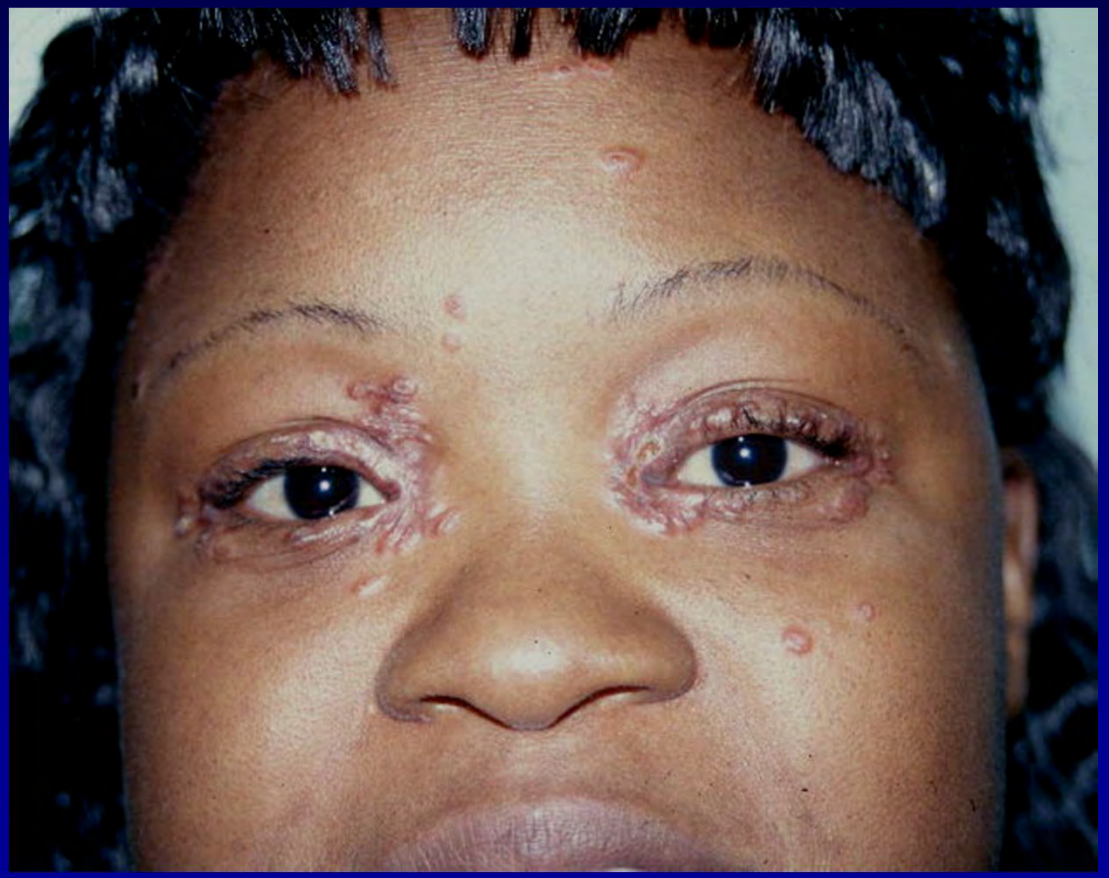
- *Lupus pernio*
- *Annular*
- *Psoriasiform*
- *Ichthyosis-like*
- *Verrucous*
- *Ulcerative*
- *Hypopigmented*
- *Nodular*
- *Micropapular*
- *Alopecia*
- *Lacrimal gland swelling*

- *ANY skin lesion not otherwise Dx should suggest sarcoidosis!*

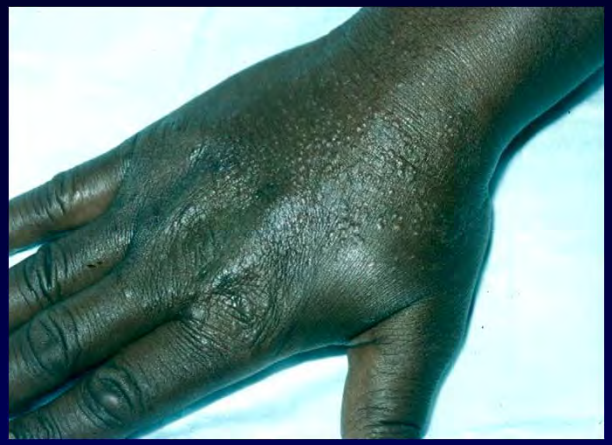
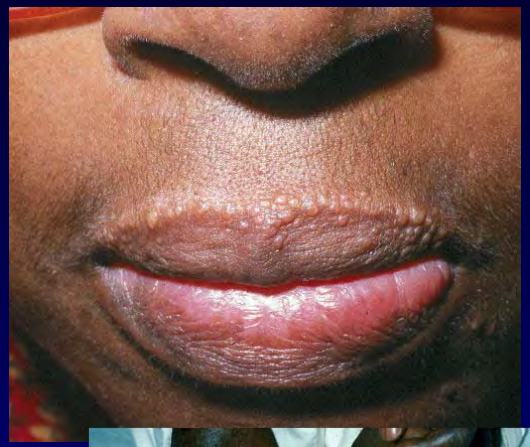
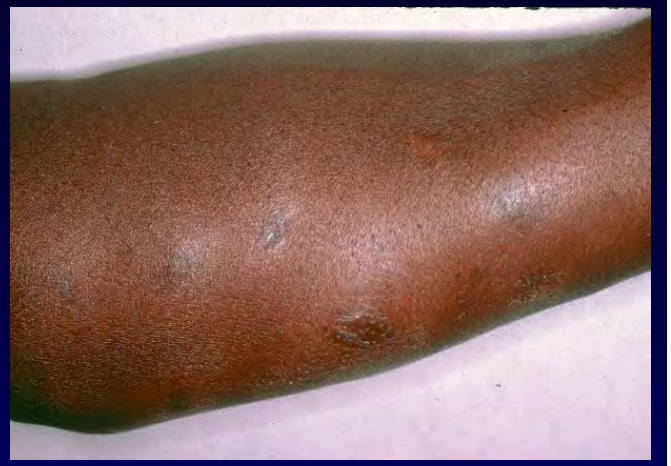
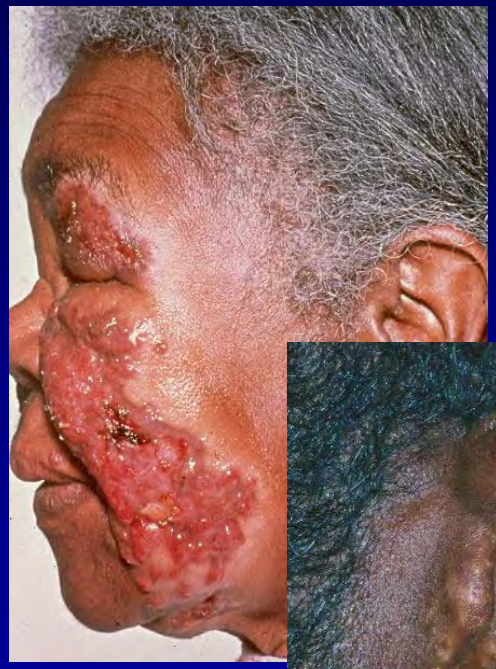
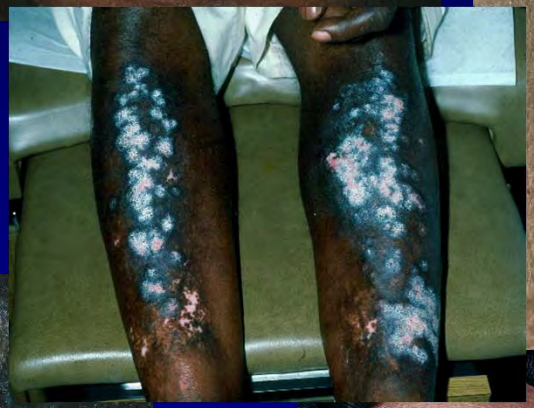
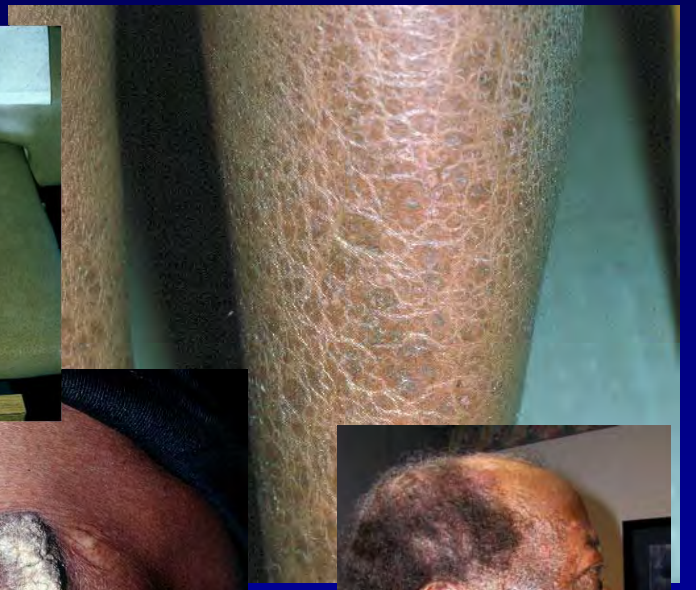
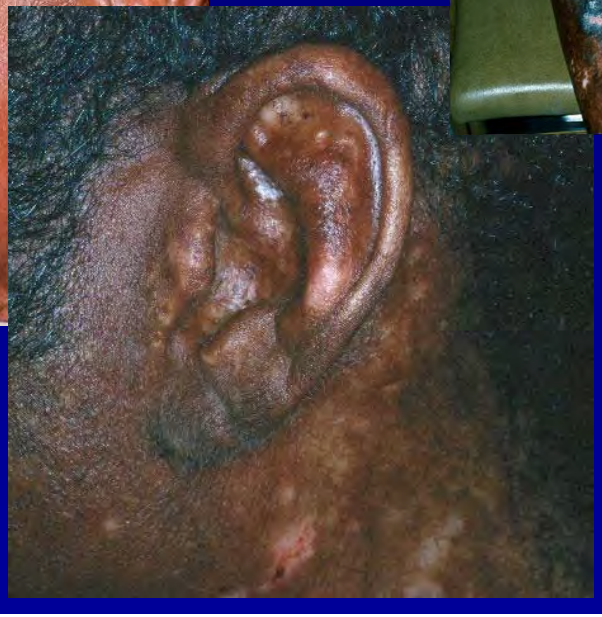
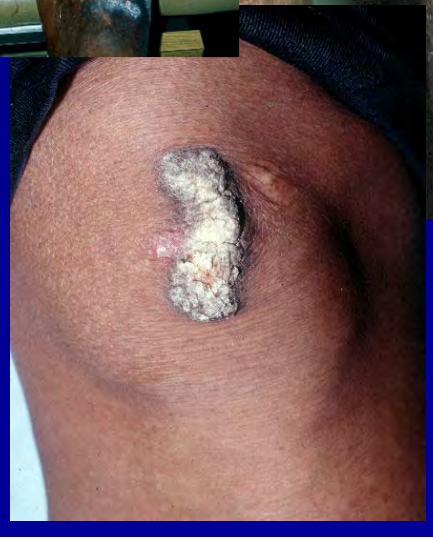

Lupus pernio

Sarcoidosis: Lupus pernio

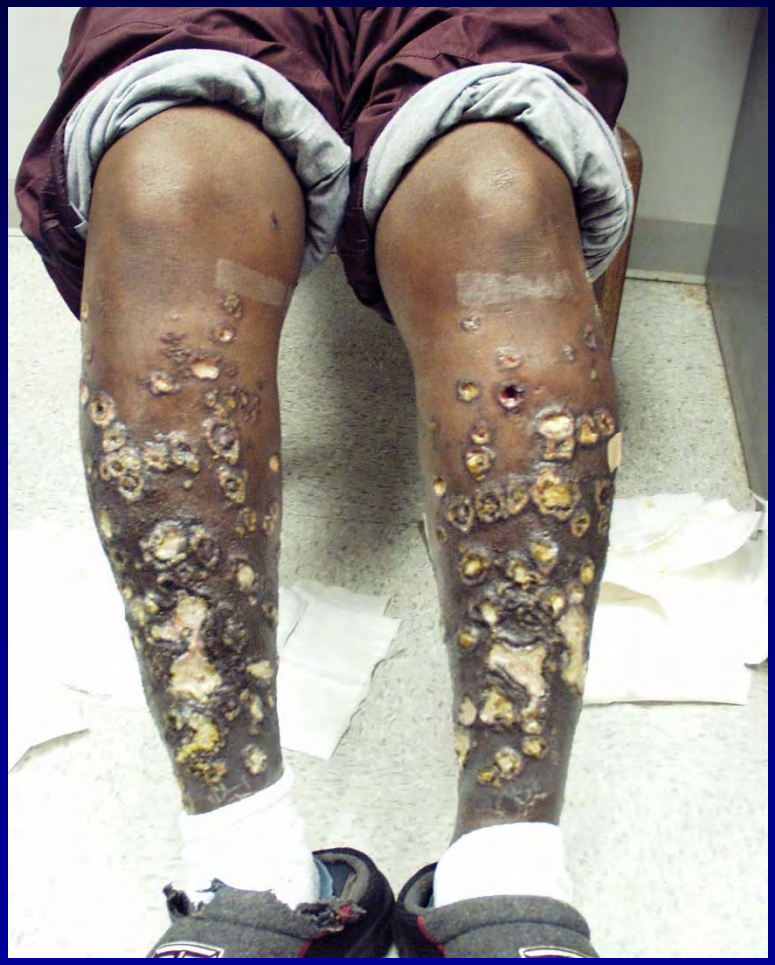


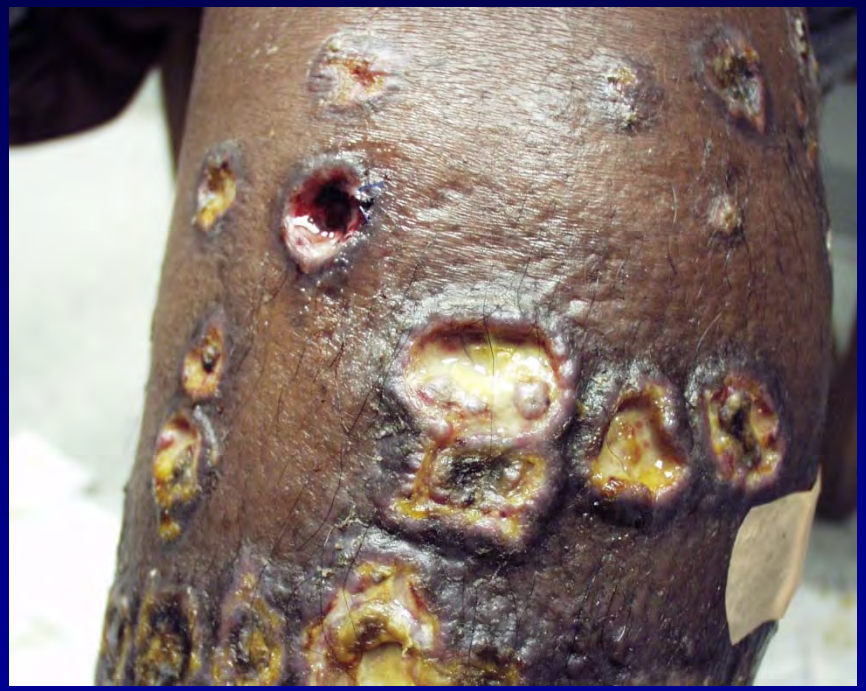


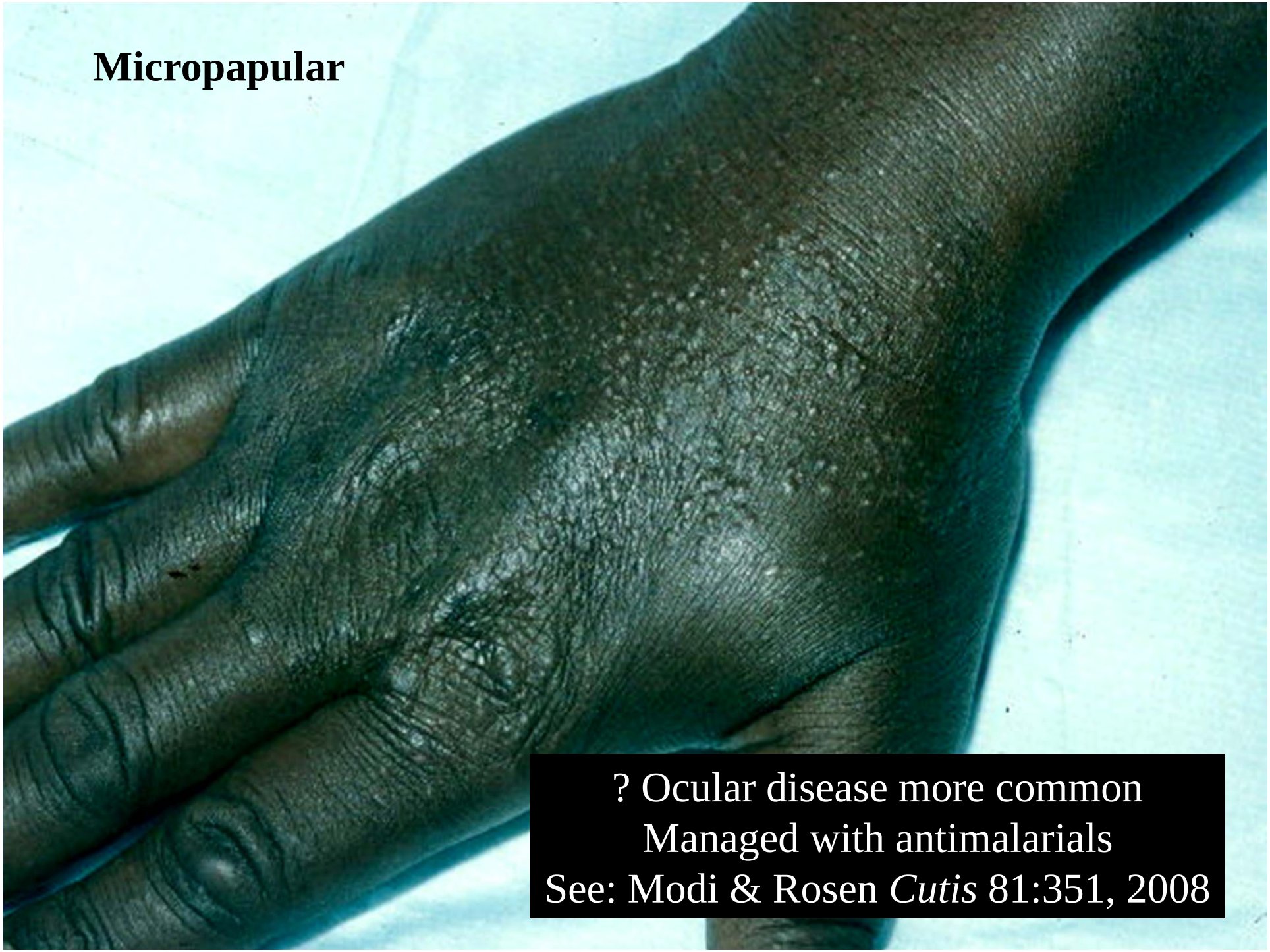
Sarcoidosis

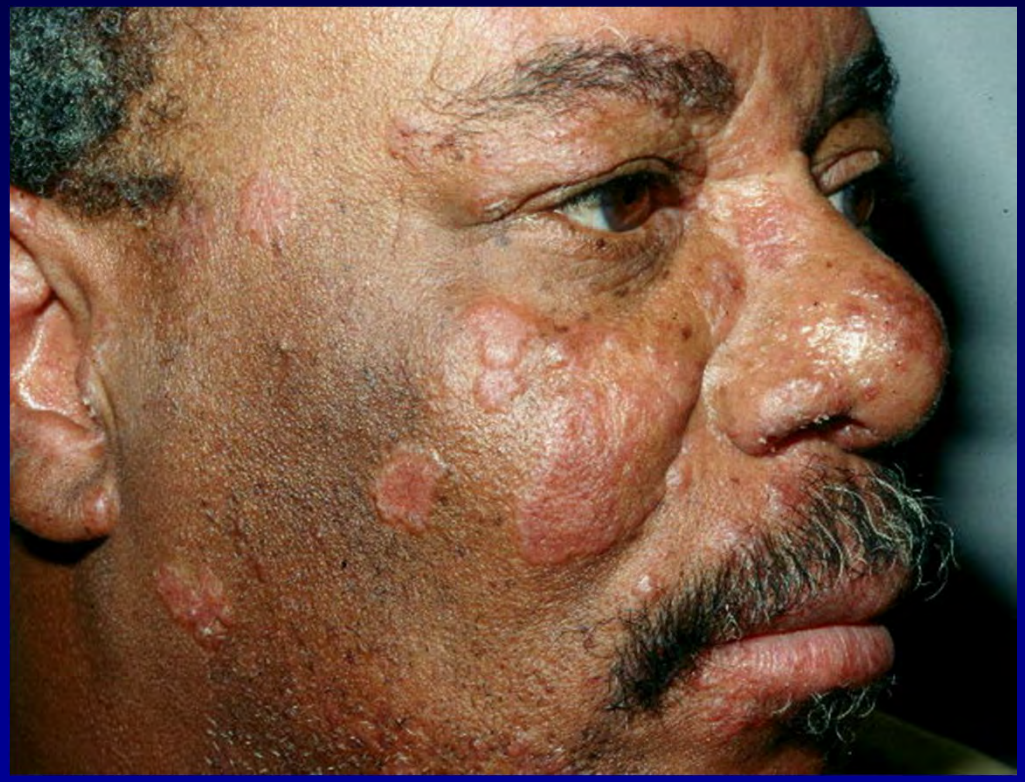

Ulcerative Sarcoid!



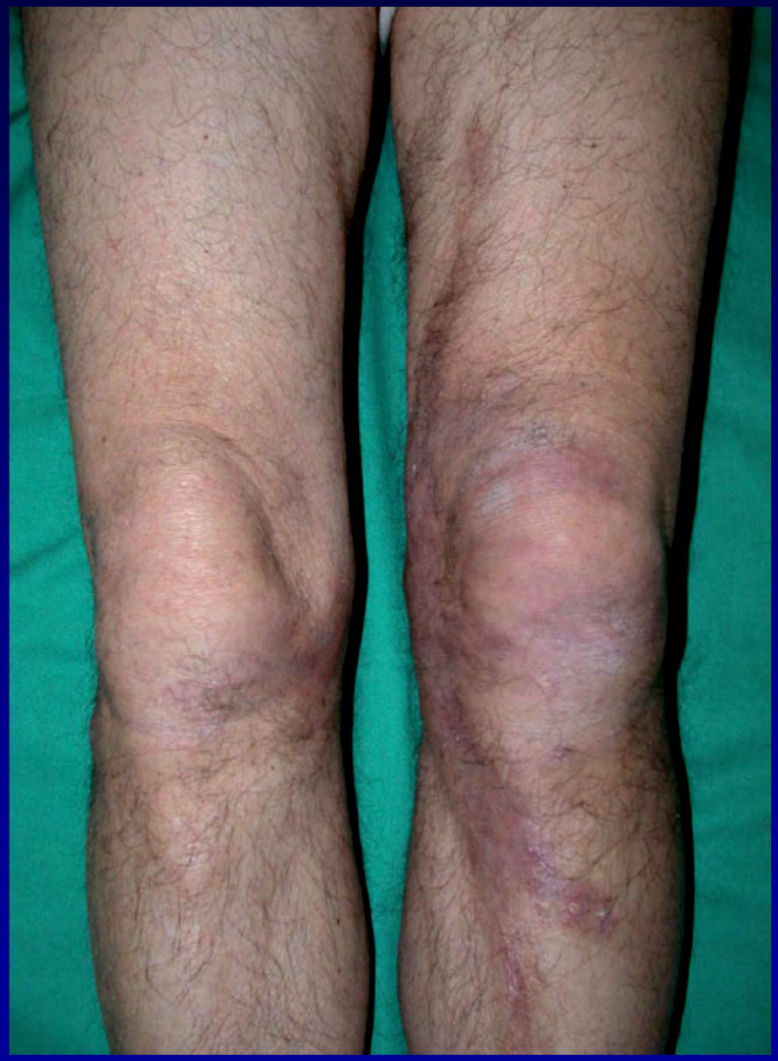


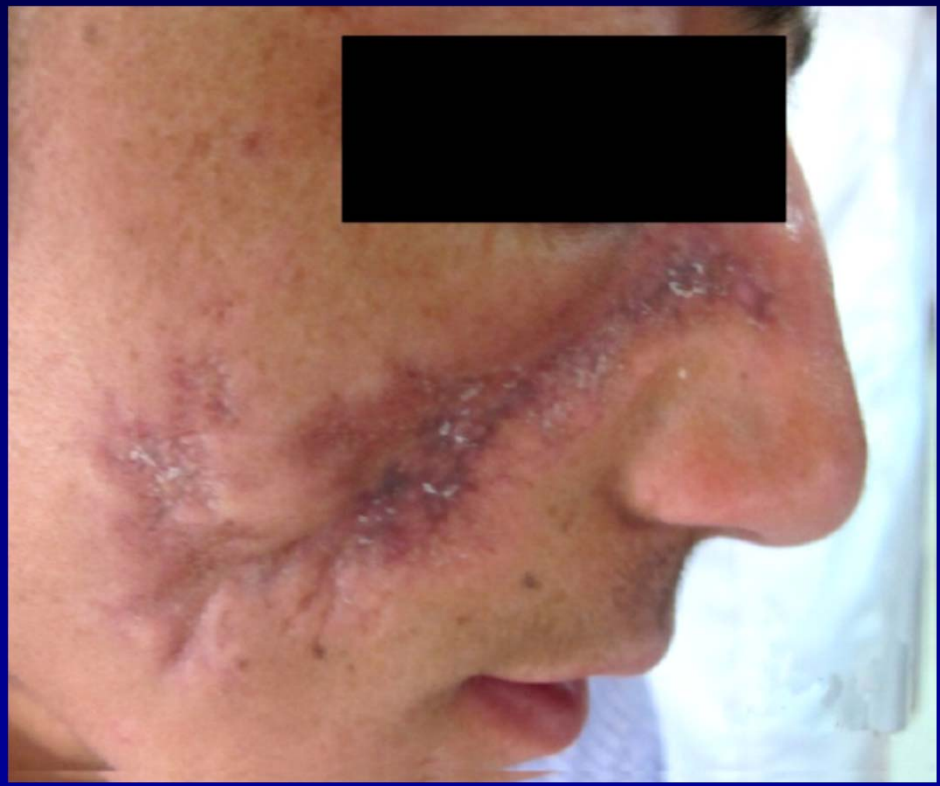

Micropapular
? Ocular disease more common
Managed with antimalarials
See: Modi & Rosen *Cutis* 81:351, 2008

Sarcoidosis: Annular Plaque

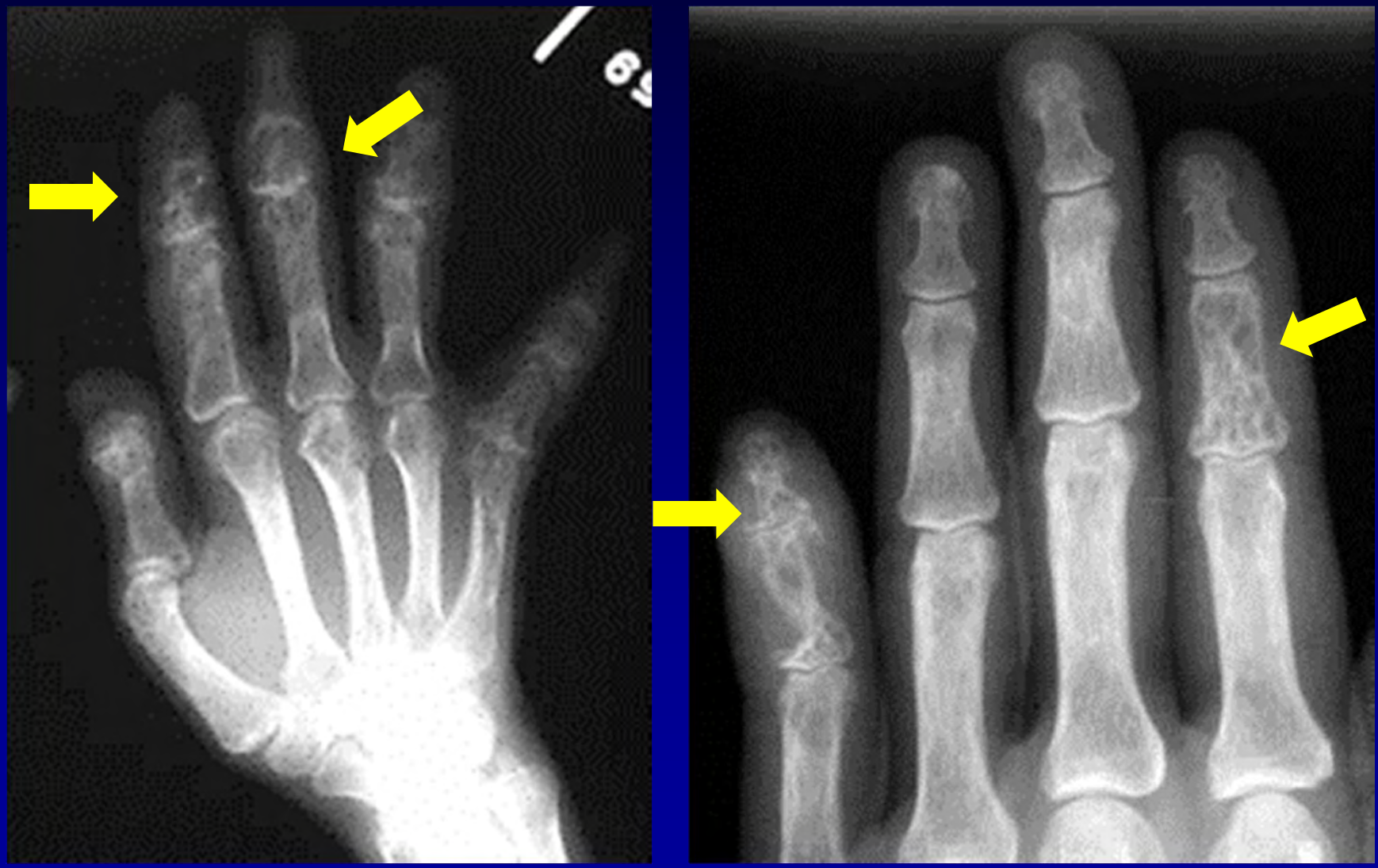


Morpheaform Sarcoid

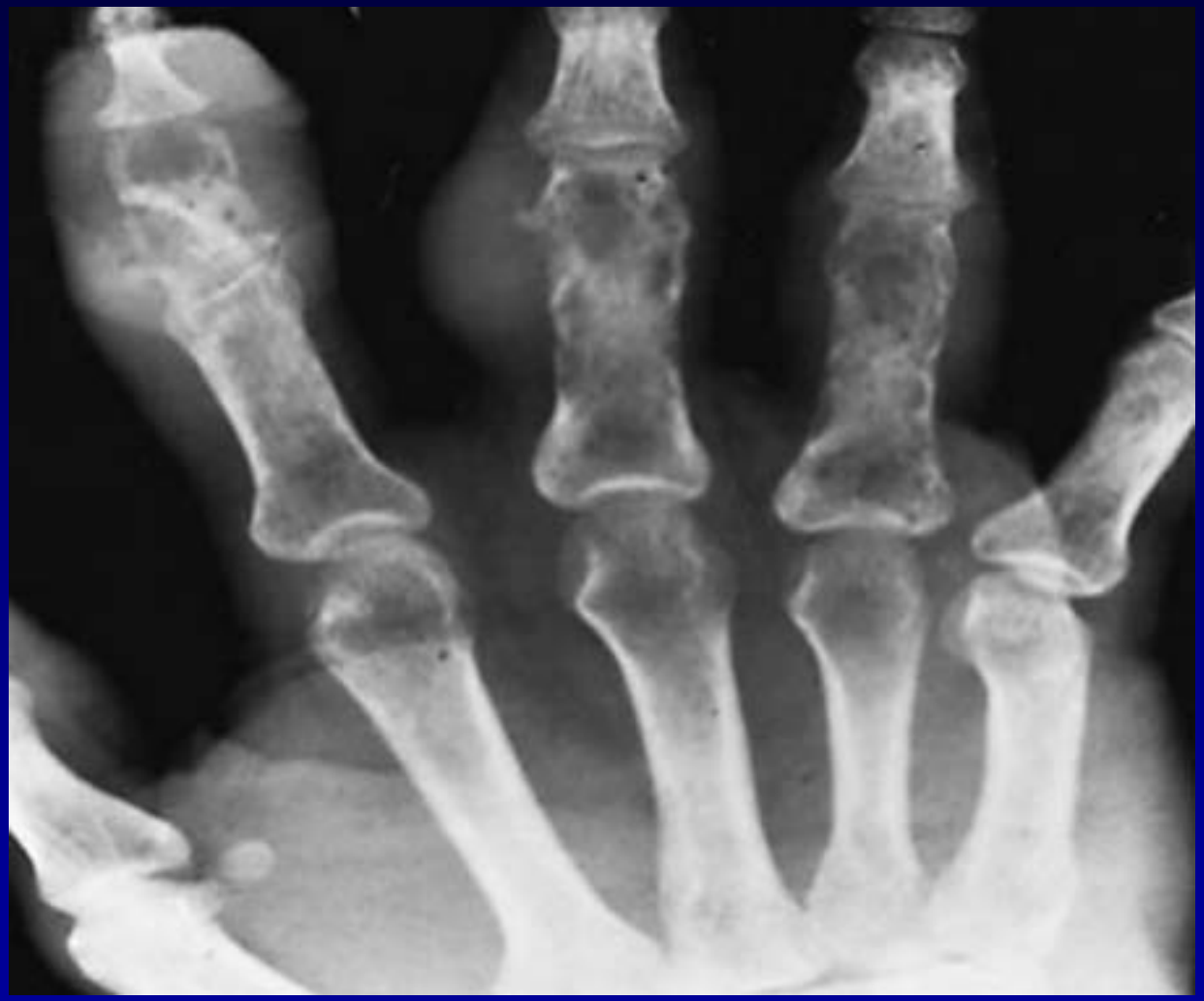




Radiograph in Sarcoid Osseous Lesions



Dactylitis
Osseous Bone Loss + Soft Tissue Swelling



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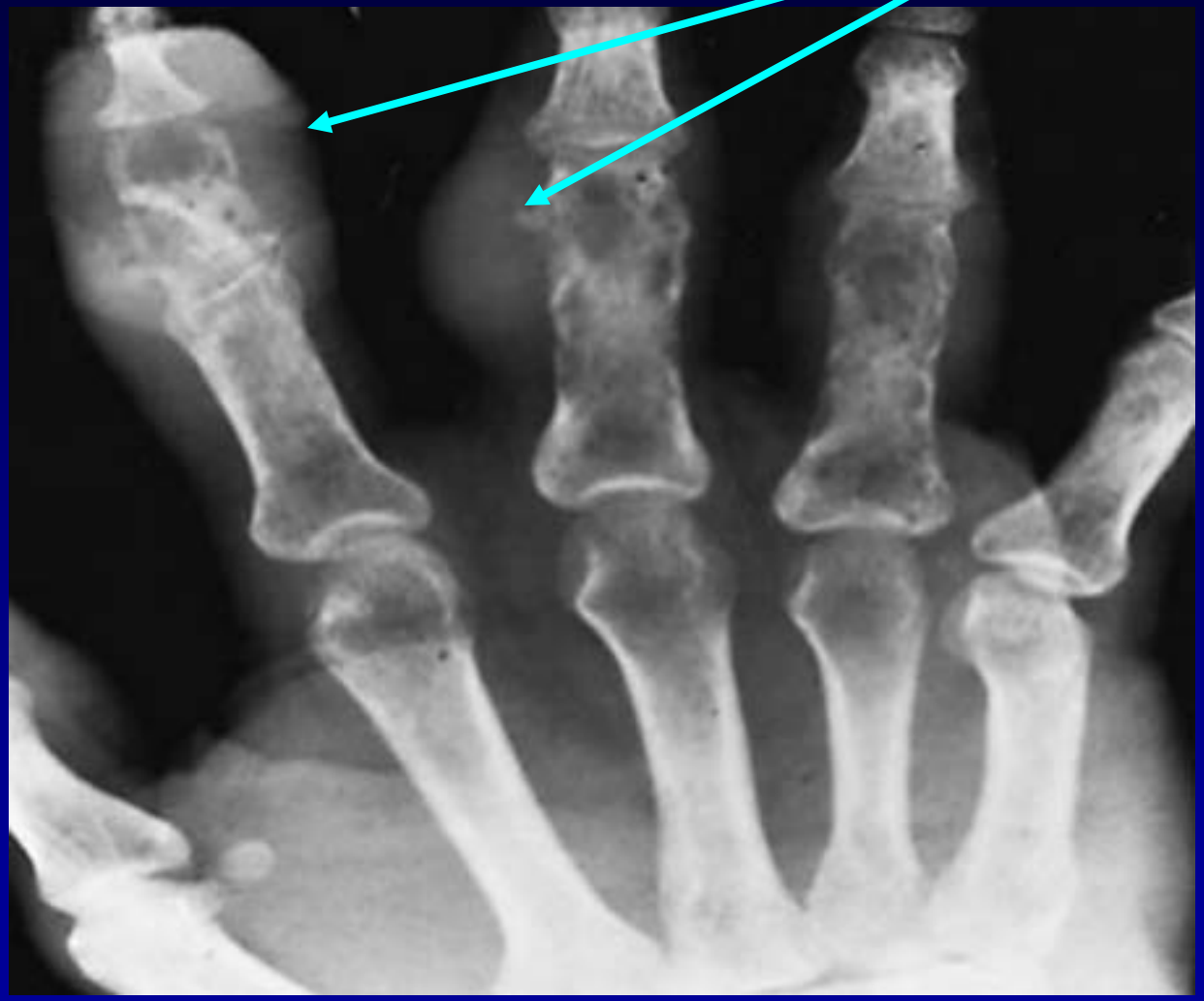

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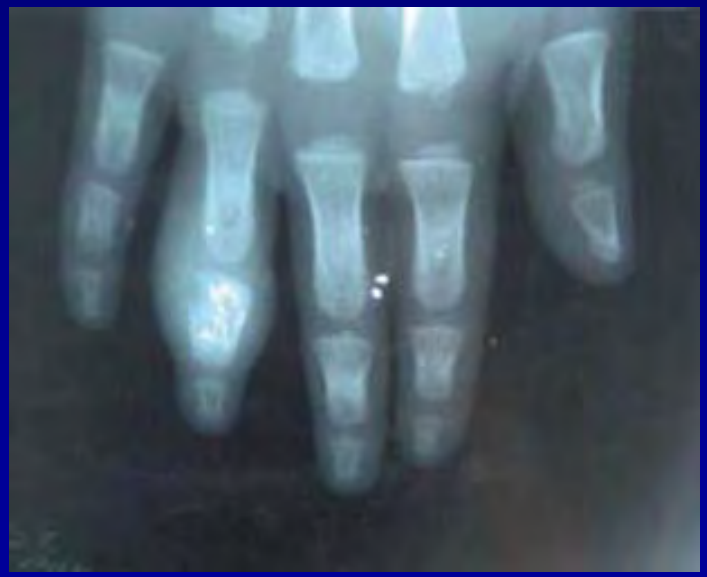
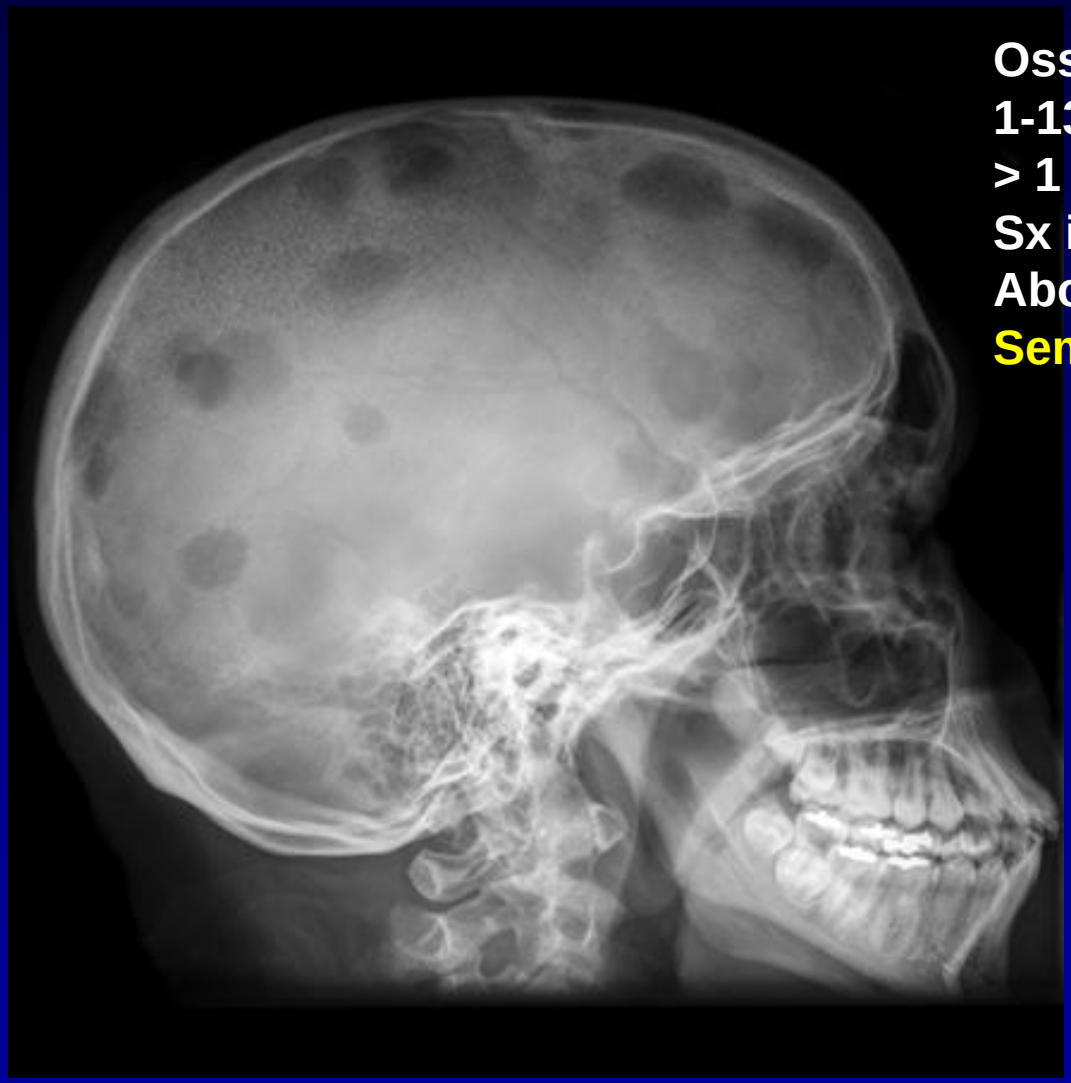


- DDx
- Psoriasis
- Sarcoidosis
- Tuberculosis
- Mycetoma
- Syphilis, Yaws
- Sickle cell dis

Lytic Bone Lesions



Osseous lesions
1-13% sarcoid patients
> 1 bone or jont involved
Sx in about 50%
About half (45%) require Rx
Semin Arthritis Rheum. 2014;44:371-9

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1-13% sarcoid patients
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Sarcoidosis: Tests to order?

- *Serum calcium and SPEP*
  (increased calcium, globulins)
- *ACE level – reflects granuloma load*
  (angiotensin converting enzyme)
- *Serum assay for soluble IL-2 R*
  (reflects activated $CD4^+$ T-cells)
- *Serum assay for MCP-1*
  (reflects activated macrophages)
- *Serum assay for soluble TNF-α R*

Respir Med 113:42, 2016
Clin Dermatol 25:303, 2007

ACE Level: Yes or NO

- *Mayo Clinic, retrospective study*
- *3277 normal matched to 285 sarcoid*
- *ACE levels compared*
- *HIGH ACE level had*
  - *Sensitivity of 41.4%*
  - *Specificity of 89.9%*
  - *PPV 25.4%*
  - *NPV 94.9%*
- *Conclusion: not reliable test for sarcoid*

Lung 194:91-5, 2016

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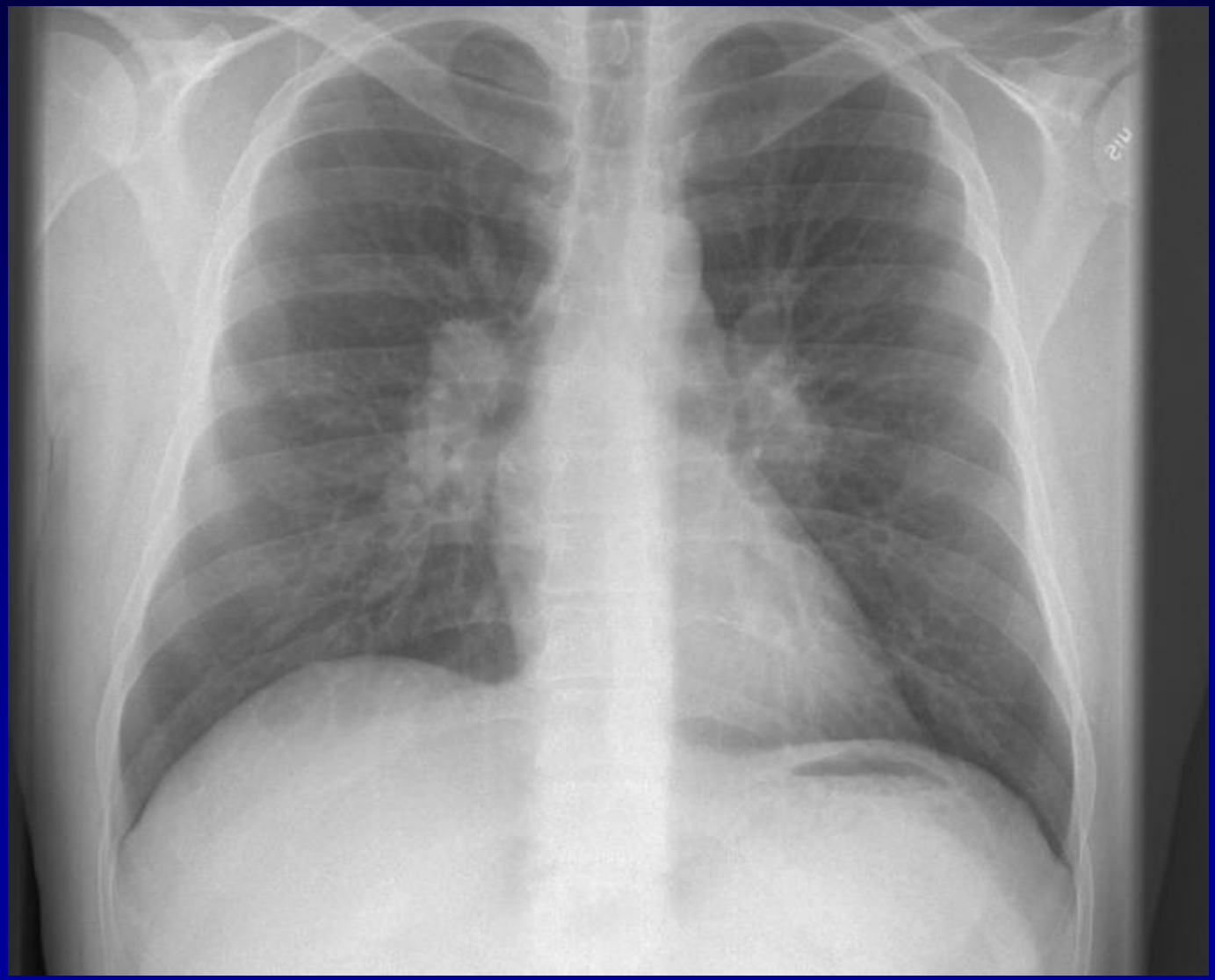
- *SCANS: MRI, CT, Gallium, PET*

Respir Med 113:42, 2016
Clin Dermatol 25:303, 2007
Clin Rev Allergy Immunol 49:45, 2015

- *CT / high resolution: mediastinal adenopathy, pulmonary parenchymal disease (>CXR) and evaluation of suspicious nodular lesions*
- *Gallium 67 and PET: overall disease activity; diagnostic workup of patients with unexplained persistent disabling symptoms; PET has replaced Gallium*
- *MRI: sensitive detection of sarcoidosis granulomata within myocardium, and differentiates sarcoid from lymphoma*
- *Role of CT in the follow-up of totally asymptomatic subjects is uncertain*

Hilar Adenopathy



CXR in Sarcoid

Stage 0: normal chest radiograph

- *5-10% of patients at presentation*

Stage I: hilar or mediastinal nodal enlargement only

- *45-65% of patients at presentation*
- *60% go onto complete resolution*

Stage II: nodal enlargement + parenchymal disease

- *25-40% of patients at presentation*

Stage III: parenchymal disease only

- *10-15% of patients at presentation*

Stage IV: end-stage lung (pulmonary fibrosis)

Clin Chest Med. 2015;36:603-19

CXR in Sarcoid

Stage 0: normal chest radiograph

- *5-10% of patients at presentation*

Stage I: hilar or mediastinal nodal enlargement only

- *45-65% of patients at presentation*

Chest radiograph does NOT necessarily correlate with the degree of functional impairment

Sta *ase*

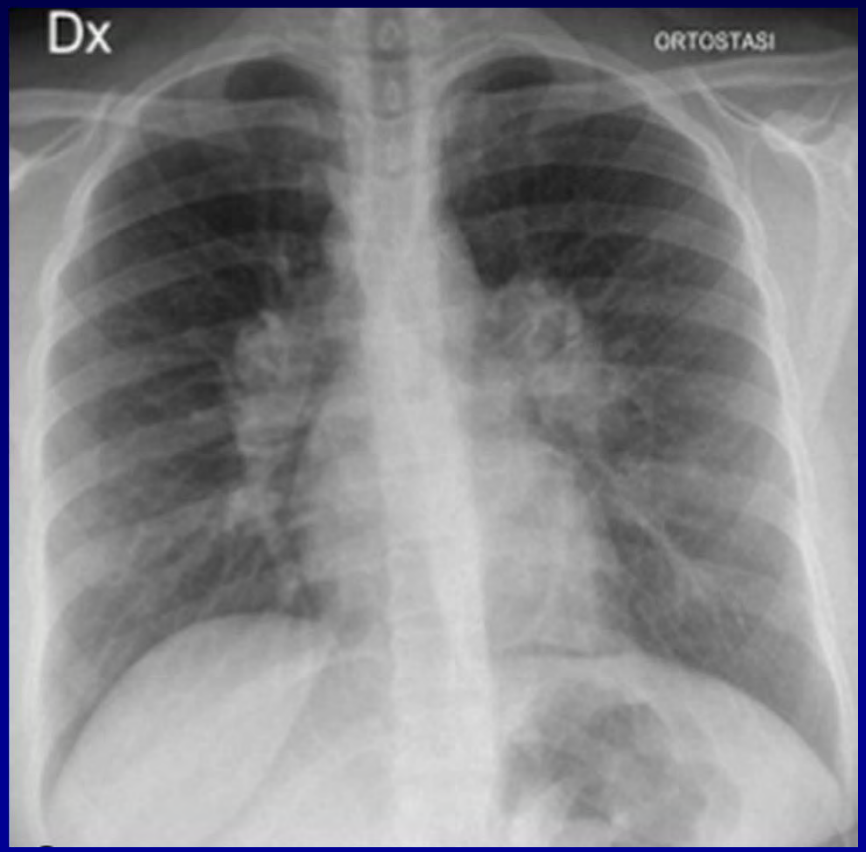
Stage III: parenchymal disease only

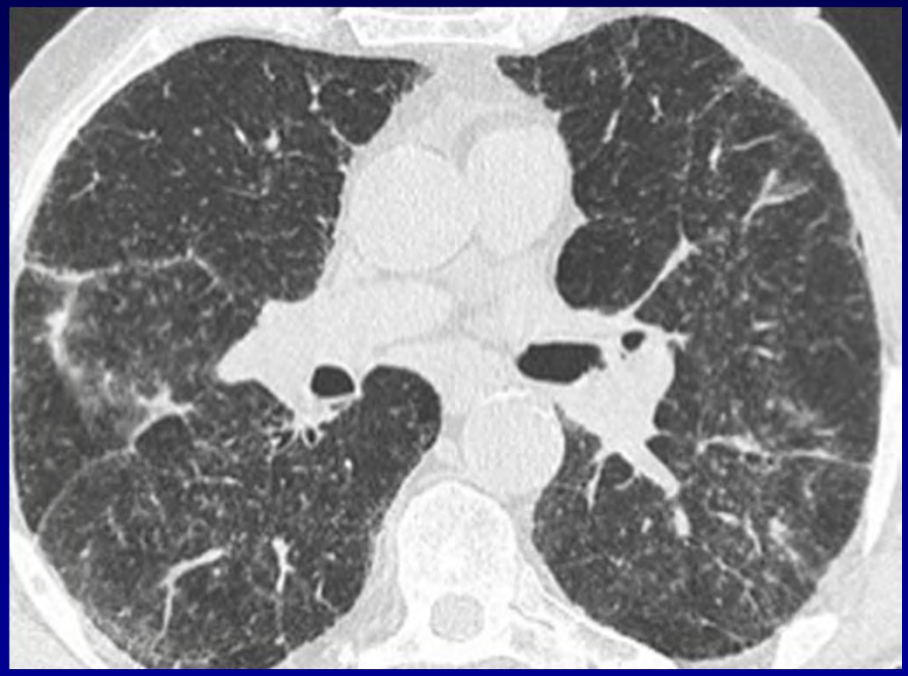
- *10-15% of patients at presentation*

Stage IV: end-stage lung (pulmonary fibrosis)

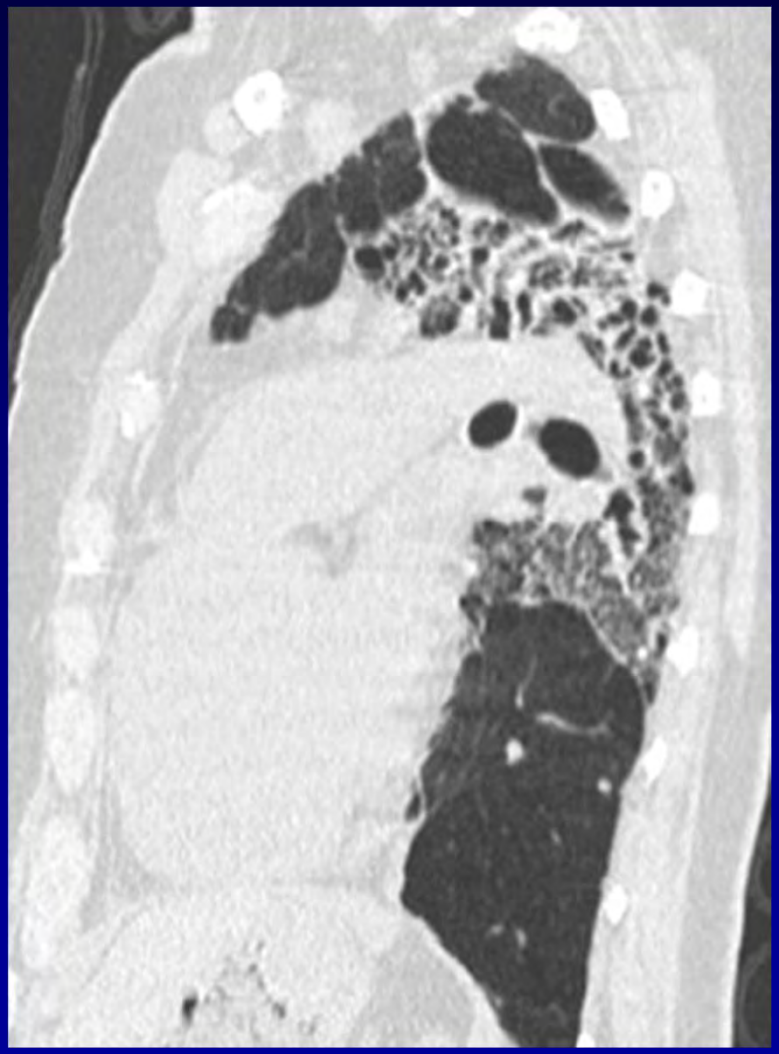
Clin Chest Med. 2015;36:603-19

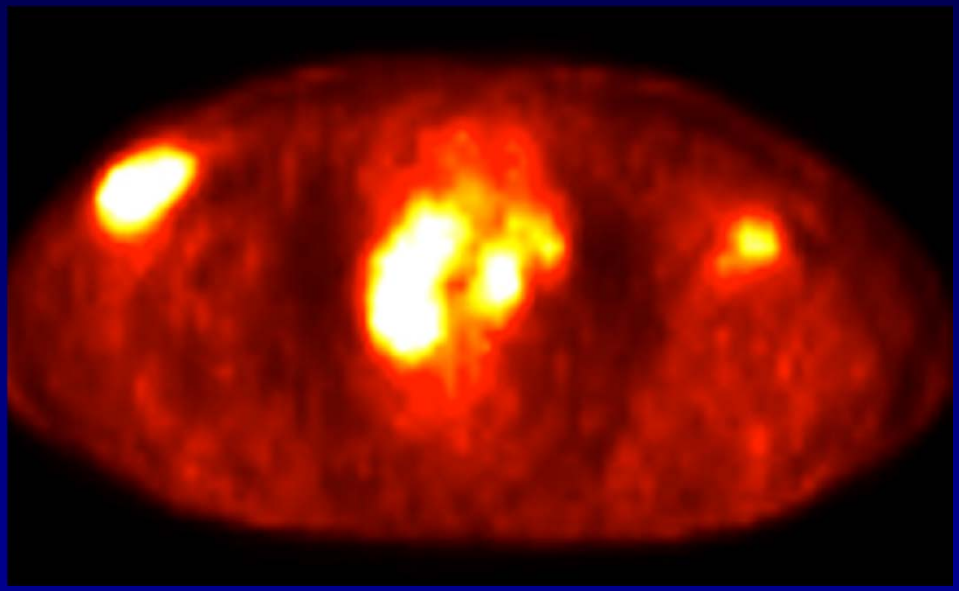
CXR versus CT Scan



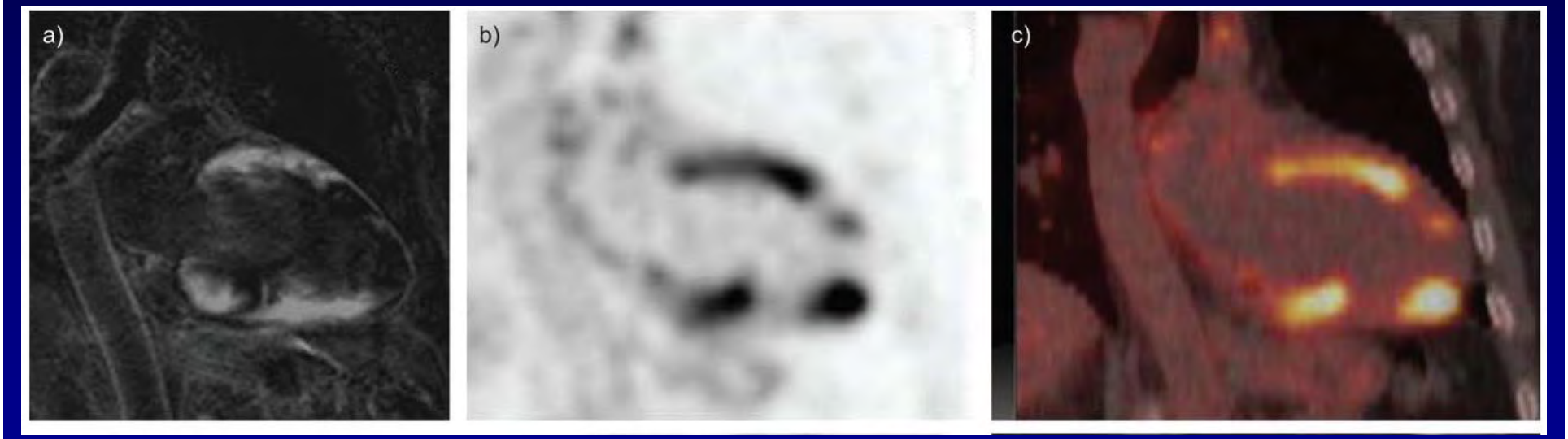


CT Scan: Fibrosis
PET Scan: "Lights up"



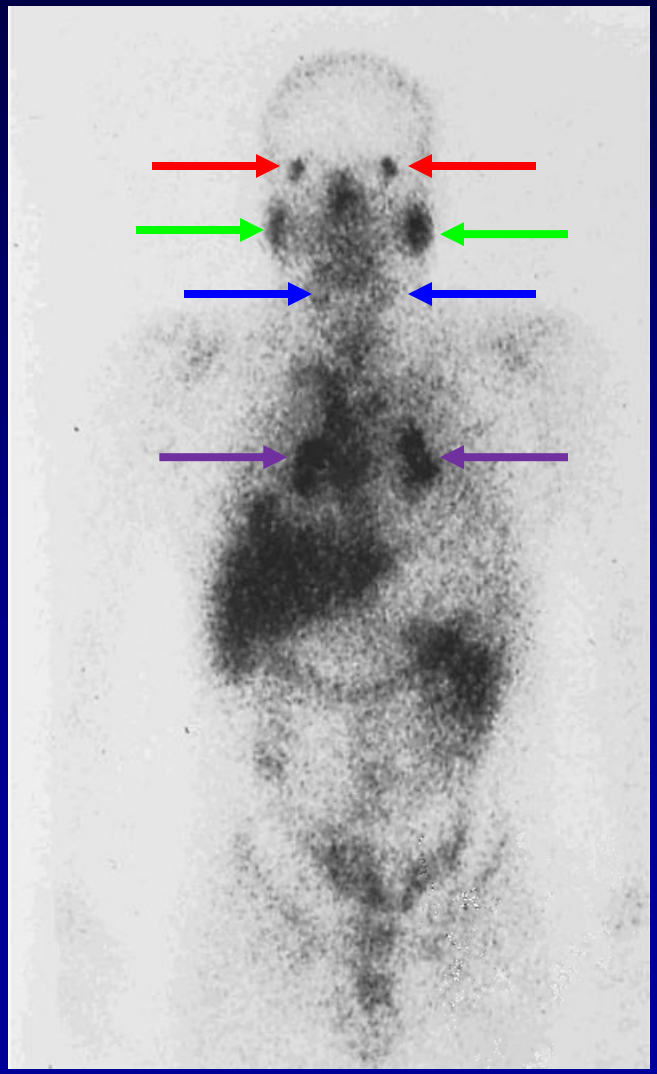


MRI + PET: Cardiac



Eur Respir J. 2013;41:743-51

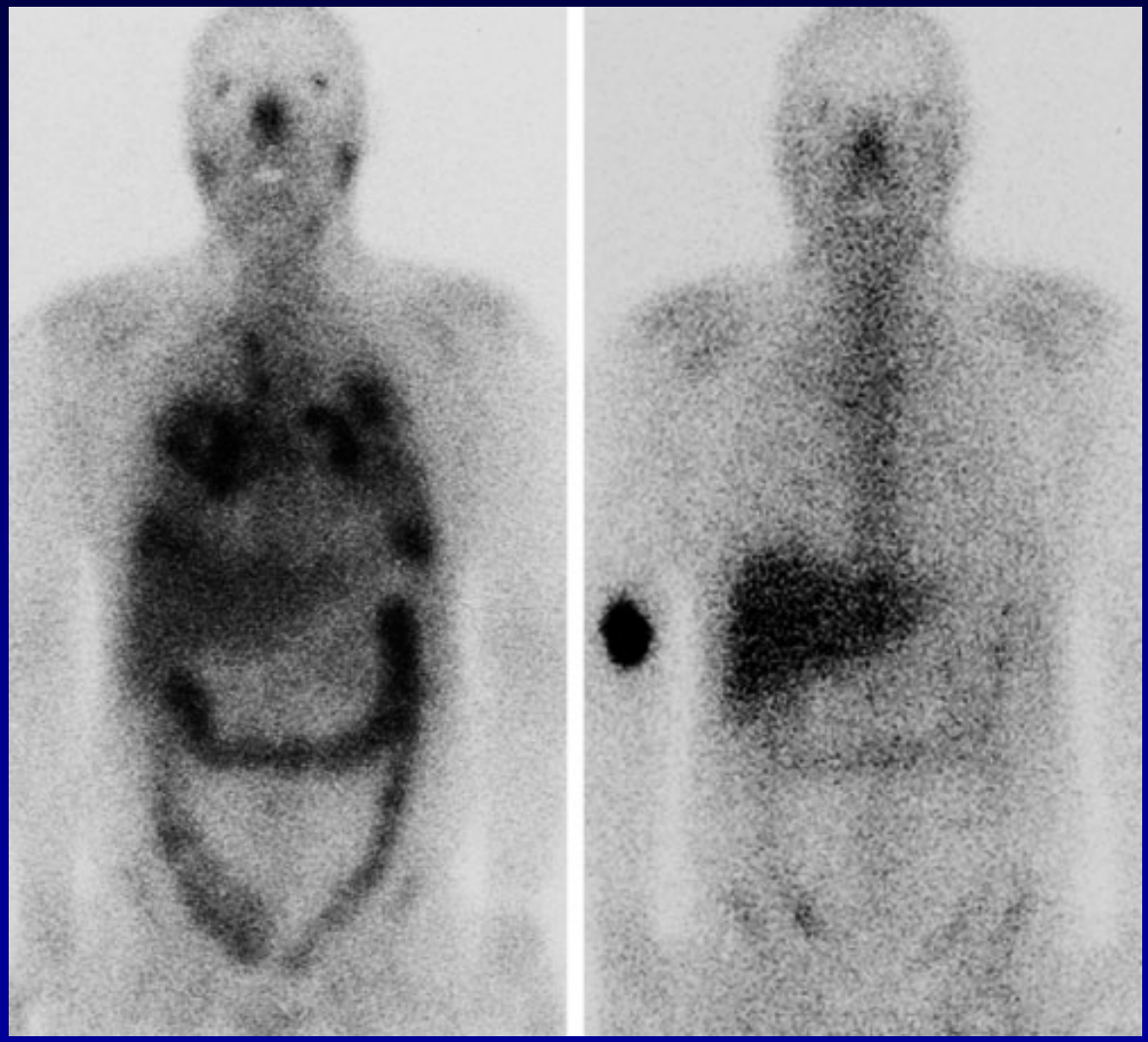
Gallium Scan



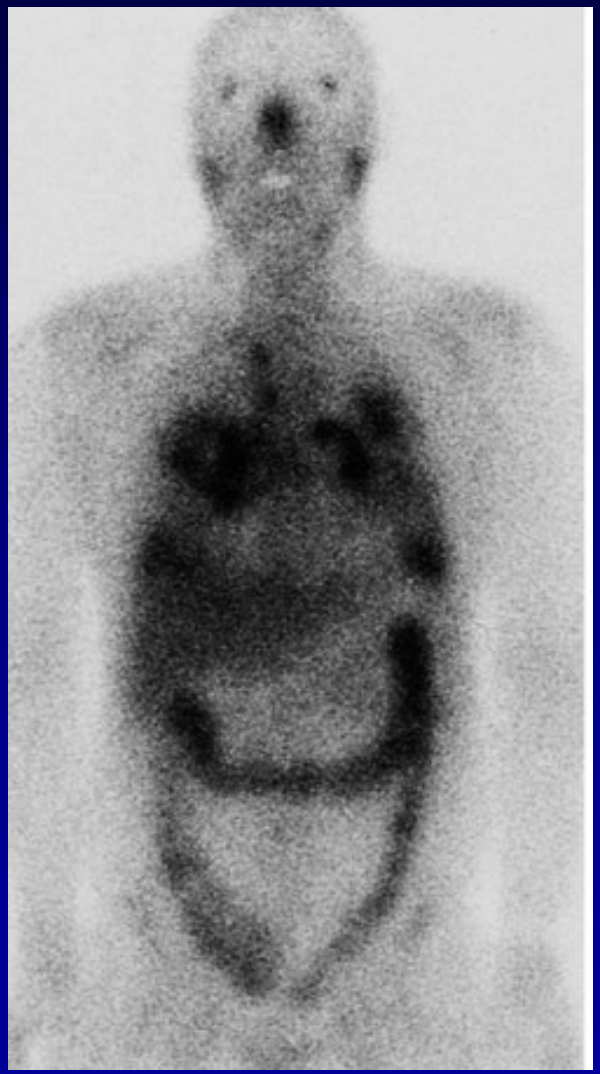
- Lacrimal gland
- Parotid gland
- Paratracheal nodes
- Hilar nodes

Gallium 67: After Rx

Clearing Pulmonary Disease



Gallium 67



“Panda Sign”

Sarcoid: Treatment

Sarcoid Therapy

- *Treatment is based upon basic science understanding of the presumed immunopathogenesis of the disorder, even though not known w/ certainty*
- *Treatment revolves around opportunities to interrupt the immunopathogenesis at various stages*

Sarcoid Pathogenesis

- *Tissue deposition of antigen*
- *Phagocytosis Ag by APC*
- *Ag + MHC presented to T cells*
- *Accumulation of clonal T-cells*
- *T-cell and APC elaboration of Th-1 subset of cytokines, chemokines*
- *Recruitment of additional cells represents amplification: granuloma*
- *Ag cleared: granuloma resolution*
- *Ag persists: fibrosis*

Presse Med 2012;41:e275-87

Sarcoidosis Therapy
Based on Pathogenesis

- *Inhibit antigen presentation*
  Antimalarial drugs
- *Suppress granuloma formation*
  Corticosteroids
  Immunosuppressives
  Anti-TNF alfa agents
- *Enhance antigen clearance*
  ? Future direction
- *Inhibit fibrosis*
  ? Corticosteroids
  ? Immunosuppressives

Sarcoidosis Therapy

- *Exhaustive summaries*
- *Evidence analyzed*
- *Paucity of RCT and even large case series; Most anecdotal*
- *Steroids, MTX, Antimalarial*
- *Doherty & Rosen Drugs 68:1361, 2008*
  Badgwell & Rosen JAAD 56:69, 2007

Sarcoid Treatment

Treatment of Sarcoidosis

Marlies S. Wijsenbeek, MD, PhD[a], Daniel A. Culver, DO[b,c,*]

KEYWORDS

• Sarcoidosis • Treatment • Corticosteroids • Steroid sparing • TNF antagonists • Prognosis
• Patient preferences

KEY POINTS

- The treatment of sarcoidosis can be divided into the key questions of "whom to treat" and "how to treat".
- The decision to treat depends on the degree of organ impairment; threat to organ function; impact of symptoms on quality of life; and the extent, activity, and chronicity of disease.
- The patient's preferences and input are central in the process of deciding when and how to treat.
- Noninflammatory manifestations of sarcoidosis are commonly the salient feature, and treatment of them is usually not with immunosuppressive medications.
- The dosing, duration, and choices of steroids and nonsteroid medications should be adjusted empirically to the individual patient.

Clin Chest Med 36:751-67, 2015

Sarcoid Treatment

- *Treatment of sarcoidosis is not required in all patients with this diagnosis*
- *In many patients with sarcoidosis, the disease resolves spontaneously*
- *Even if the disease persists, it may not cause sufficient problems to require therapy*
- *Survey of 500 patients, 10 centers worldwide: only 43% still require Rx 5 years after diagnosis*

Clin Chest Med 36:751-67, 2015
Sarcoidosis Vasc Diffuse Lung Dis 28:56–64, 2011

Before ANY Therapy…

- *Assess extent of disease*
  - *Which organ system(s)*
  - *Sarcoidosis Vasc Diffuse Lung Dis 31:19–27, 2014*
- *Assess severity of disease*
  - *Deviation from normal physiology*
  - *Curr Opin Pulm Med 20:496–502, 2014*
- *Assess activity of disease*
  - *Continuing functional deterioration*
- *Assess impact on patient lifestyle*
  - *Specific questionnaires*
  - *Am J Respir Crit Care Med 191:786–95, 2015*

Sarcoid
Standard Therapy

- ***Corticosteroids***
  Oral (Prednisone 20-80mg/day)
  Intra-lesional (3-20mg/ml TAC)
  Topical (Ultrapotent)
- ***Antimalarial drugs***
  Chloroquine 4.0mg/kg/day
  Hydroxychloroquine 6.5mg/kg/day
- ***Methotrexate***
  10-30mg weekly

Corticosteroids and Sarcoid

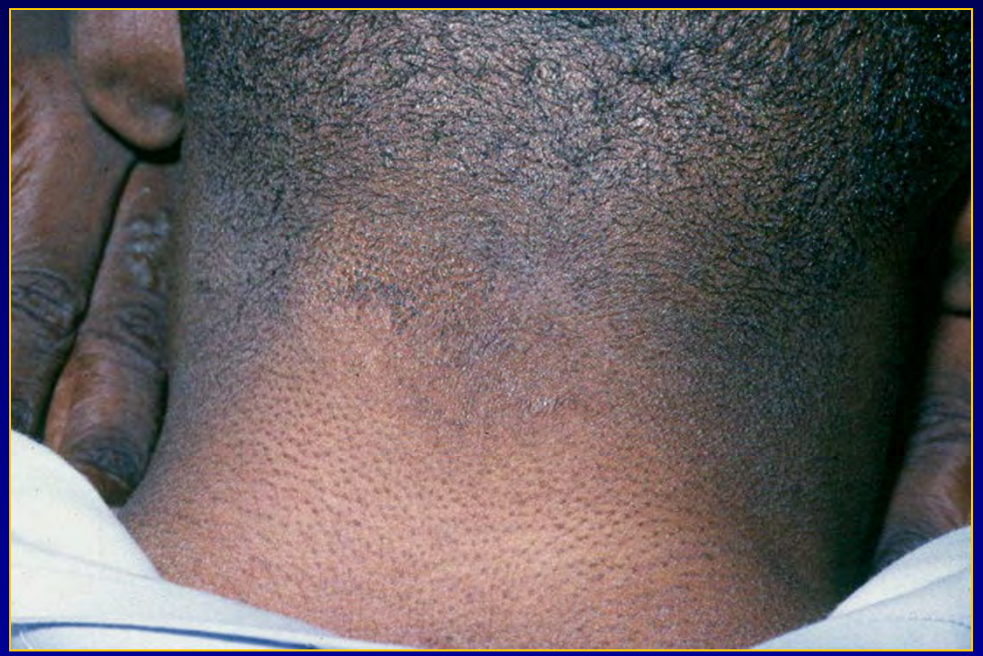
- *Treatment indicated if: the disease causes a dangerous health situation or significantly ↓QOL*
- *Treatment not be based on biomarkers of active granulomatous inflammation*
- *Corticosteroids almost always effective*
- *It is unusual for patients to be refractory to corticosteroid therapy*
- *Alternative medications are often employed because of the frequent development of corticosteroid toxicity*

Rheum Dis Clin North Am 42:119-35, 2016

Antimalarials and Sarcoid

- *No RCT for skin disease (lung-yes)*
- *Isolated case reports and small series*
- *Often used due to low toxicity risk*
- *Low cost, easy administration*
- *Dermatol Online J. 2014 Jan 15;20(1):21250*
  Hautarzt. 2011;62:691-5
  Cutis. 2008;81:351-4
  Isr Med Assoc J. 2000;2:558-9
  Am J Respir Crit Care Med. 1999;160:192-7
  Arch Neurol. 1998;55:1248-54
  Clin Exp Dermatol. 1994;19:448
  Arch Dermatol. 1991;127:1034-40

Sarcoidosis



Hydroxychloroquine 200mg BID

Antimalarials and Sarcoid

- *Ocular toxicity: Parameters to consider*
- *Chloroquine 3.0mg/kg/d max*
  Hydroxychloroquine 6.5mg/kg/d max
- *Chloroquine 460g cumulative dose*
  Hydroxychloroquine 1000g cumulative
- *Eye screen: Visual fields or objective tests:*
  Spectral Domain-Optical Coherence Tomography
  Fundus Autofluorescence; Multifocal Electroretinography
- *Eye screen: Baseline, 5Yrs, <u>then</u> Yearly*

Dermatol Online J. 2014 Jan 15;20(1):21250
Ophthalmology, 2011;118: 415–422
Hautarzt. 2011;62:691-5
Cutis. 2008;81:351-4

Antimalarials and Sarcoid

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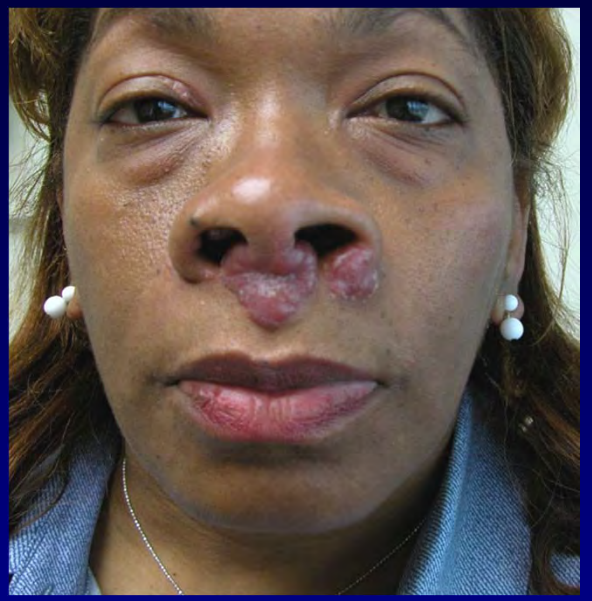
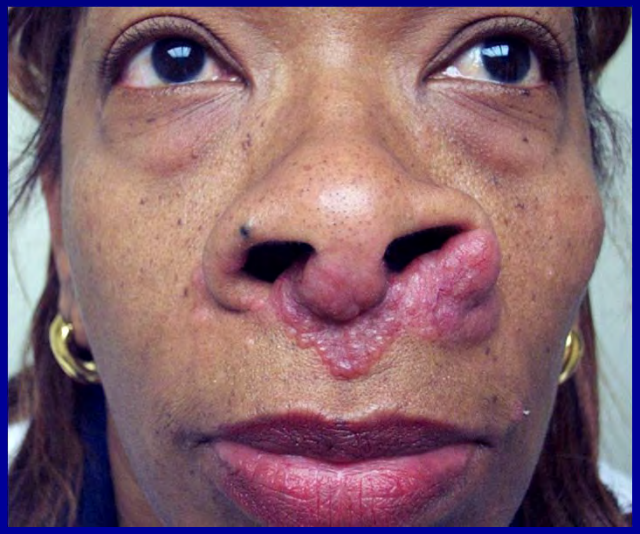
Dermatol Online J. 2014 Jan 15;20(1):21250
Ophthalmology, 2011;118: 415–422
Hautarzt. 2011;62:691-5
Cutis. 2008;81:351-4

What if "standard" therapy doesn't work or is not tolerated?

- *Failed prednisone at 60mg/d (↑BP)*
- *Failed MTX 30mg/wk*
- *Failed chloroquine & hydroxychloroquine at maximal doses*
- *Potent topical steroids: no change*
- *IL steroid: minimal improvement*





Pentoxifylline

- *Why in sarcoid?*
- *Inhibits TNF-α release from tissue and peripheral blood monocytes and macrophages (critical for granuloma persistence)*
- *Immun Infect 23:107, 1995*
  Am J Resp Crit Care Med 159:508, 1999
  Chest 124:1526, 2003
  Chest 126:321, 2004
  Sarcoidosis Vasc Diffuse Lung Dis 26:121, 2009

Pentoxifylline

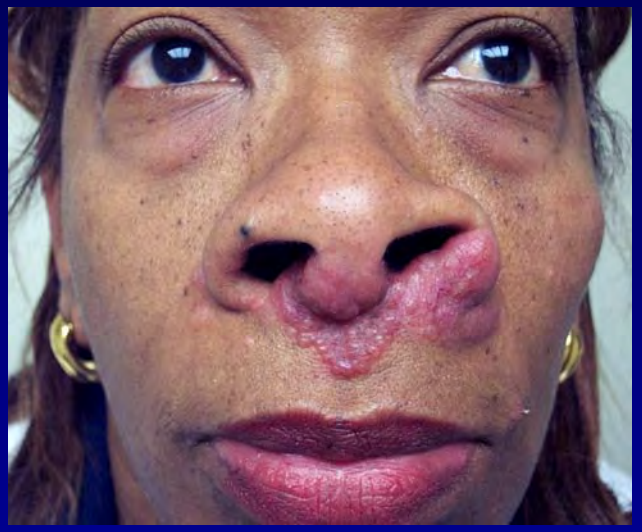
- *Does it work?*
- *One open-label study*
- *Pulmonary sarcoid*
- *11/18 improved pulmonary functions and symptomatology*
- *25mg/kg dose*
- *Am J Respir Crit Care Med 155:1665, 1997*
- *Concerns: GI intolerance; mild bleeding diathesis*

Pentoxifylline

- *Does it work? Maybe*
- *RCT for 10 months; 25mg/kg dose*
- *Pulmonary sarcoid n=27*
- *NONE had sustained improvement in pulmonary functions, but...*
- *Lower steroid dose, fewer flares*
- *Sarcoidosis Vasc Diffuse Lung Dis. 2009;26:121-31*
- *Concerns: No major AEs*

Pentoxifylline

- *Failed pentoxifylliine at full doses given for 6 months*



Tetracycline Derivatives

- *Why in sarcoid?*
- *TCN derivatives downregulate ICAM-1 expression, decreasing accumulation of T-cells*
- *TCN derivatives downregulate IL-2 and chemokine secretion, decreasing activation of T-cells*
- *TCN derivatives interfere with matrix metalloproteinases (mediate tissue damage)*
- *Minocycline ↓TNF-α (synthesis, release)*
- *Am J Physiol - Renal Physiol 287:F760, 2004*
  SkinMed 2:234, 2003

OR.....

Tetracyclines

- *Why in sarcoid?*
- *Could the causative antigen be a bacterium? In particular, a cell wall deficient acid-fast bacterium.....*
- *Autoimmun Rev 3:295, 2004*

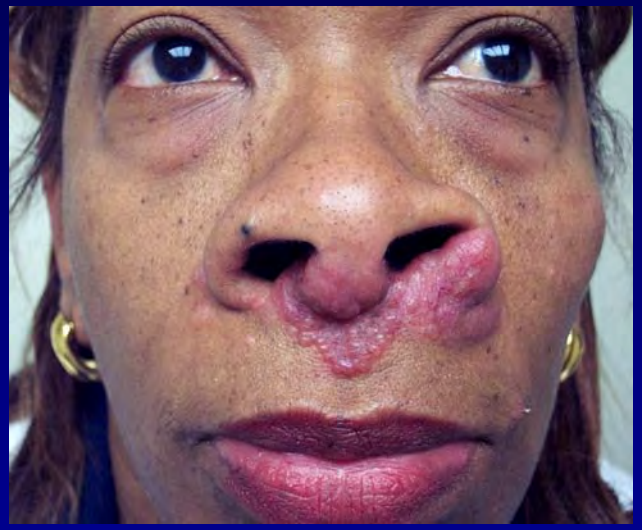
Minocycline in Sarcoid

REFERENCE	RESPONDED?	COMMENT
Dermatol Online J 2014 Aug 17;20(8)	1 of 1	Skin only
JAMA Dermatol 2013;149:758-60	20 of 27	Skin only
J Drugs Dermatol 2012;11:385-89	1 of 1	Hypopigmented
Clin Rheumatol 2008;27:1195-97	1 of 1	Ocular + Lung
Arch Ophthalmol 2007;125:705-09	1 of 1	Ocular + Skin
Arch Dermatol 2001;137:69-73	10 of 12	Skin only

- **All at dose of 200mg/day**

Tetracyclines

- *Failed doxycycline 200mg/d*
- *Failed minocycline 200mg/day*



Isotretinoin

- Why in sarcoid?
- Immunomodulatory activity?
  Not well characterized
- Suppresses T-cell response to antigenic stimulus (proliferation)
- Decreases release of IL-2
- ? Decreases antigen presentation
- J Invest Dermatol 93:455, 1989
  J Clin Invest 88:1331, 1991

Isotretinoin

- *Does it work?*
- *Three cases reports with partial to complete response (skin)*
- *1mg/kg/d but given for many months to achieve results*
- *One case with persistent remission (~1 year)*
- *Arch Dermatol 119:1003, 1983*
  Ann Derm Venereol 113:1089, 1986
  Acta Derm Venereol 78:457, 1998

Leflunomide

- *Why in sarcoid?*
- *Inhibits pyrimidine synthesis; proliferating T-cells expand their pyrimidine pool 8x if multiplying*
- *Decreases TNF-α response via tyrosine kinase inhibition*
- *Reduces cell-cell contact activation and thereby inhibits monocyte activation by proliferating T-cells*
- *Ann Rheum Dis 59:841, 2000*

Leflunomide

- *Does it work?*
- *Case report: skin and respiratory*
  Rheumatology 45:700, 2003
- *Case series: 80% of 32 patients with skin/eye/lung respond*
  Sarcoid Vasc Diffuse Lung Dis 21:43, 2004
- *Concerns: nausea, headache, hypersensitivity (EM, Exfol Derm, SJS) hepatic injury (may be severe)*
  J Dermatol 30:845, 2003
  Dermatology 207:356, 2003

Thalidomide

- *α-N-phalidimodo-glutaramide*
- *Developed by CIBA (Swiss) but disontinued in 1953 (“non-therapeutic”)*
- *1954 Chemie Grunenthal (Germany)*
  -Sedative-hypnotic inducing deep sleep
  -Rapid onset with no hangover effect
- *14 companies marketed in 46 countries*
- *1960-62 Phocomelia (other defects)*
- *1965 Dramatic response ENL (Israel), verfied by WHO blinded study (1967)*
- *1970’s: aphthosis, LE*
- *1980’s: Neutrophilic dermatoses, sarcoid, GVH*

Thalidomide

- *Why in sarcoid?*
- *Decreases TNF-α by accelerating degradation of mRNA for this critical cytokine (net: decreased production)*
- *Decreases interferon gamma production*
- *Decreases surface adhesion molecules*
- *Decreases circulating T-cell number*
- *J Exp Med 177:1675, 1993*
  J Exp Med 173:699,1991
  Clin Exp Immunol 99:160, 1995

Thalidomide

- *Does it work?*
- *Isolated case reports skin and lung demonstrate efficacy at 50-200mg/d*
  Presse Med 12:963, 1983
  JAAD 32:866, 1995
  Arch Dermatol 134:1045, 1998
  Rev Med Intern (French) 19:208, 1998
  JAAD 39:835, 1998
  Biomed Pharmacother 66:300, 2012
- *One series where 10/12 show partial or complete response to drug*
  JAAD 50:235, 2004

BUT....

[Original Research **Diffuse Lung Disease**]

CHEST

True RCT; Thalidomide 100mg/d vrs placebo

A Randomized, Investigator-Masked, Double-Blind, Placebo-Controlled Trial on Thalidomide in Severe Cutaneous Sarcoidosis

Catherine Droitcourt, MD; Michel Rybojad, MD; Raphaël Porcher, PhD; Caroline Juillard, MD; Anne Cosnes, MD; Pascal Joly, MD, PhD; Jean-Philippe Lacour, MD, PhD; Michel D'Incan, MD, PhD; Nicolas Dupin, MD, PhD; Bruno Sassolas, MD; Laurent Misery, MD, PhD; Jacqueline Chevrant-Breton, MD; Bénédicte Lebrun-Vignes, MD; Kristell Desseaux, MSc; Dominique Valeyre, MD, PhD; Jean Revuz, MD; Abdellatif Tazi, MD, PhD; Olivier Chosidow, MD, PhD; and Alain Dupuy, MD, PhD

Chest. 2014;146:1046-54.

BACKGROUND: Thalidomide use in cutaneous sarcoidosis is based on data from small case series or case reports. The objective of this study was to evaluate the efficacy and safety of thalidomide in severe cutaneous sarcoidosis.

METHODS: This study consisted of a randomized, double-bind, parallel, placebo-controlled, investigator-masked, multicenter trial lasting 3 months and an open-label study from month 3 to month 6. Adults with a clinical and histologic diagnosis of cutaneous sarcoidosis were included in nine hospital centers in France. Patients were randomized 1:1 to oral thalidomide (100 mg once daily) or to a matching oral placebo for 3 months. In the course of an open-label follow-up from month 3 to month 6, all patients received thalidomide, 100 mg to 200 mg daily. The proportions of patients with a partial or complete cutaneous response at month 3, based on at least a 50% improvement in three target lesions scored for area and infiltration, were compared across randomization groups.

Thalidomide in Sarcoid

- *European RCT, multi-center, three months*
- *Thalidomide 100mg/d vrs Placebo 1:1*
- *ITT population = 39 (20 active, 19 placebo)*
- *At month three, 20% T vrs 21% Placebo demonstrated response (none complete)*
- *EIGHT of TWENTY on thalidomide D/C due to adverse events*
- *"Our results do not encourage thalidomide use in cutaneous sarcoidosis."*

Chest 146:1046-54, 2014

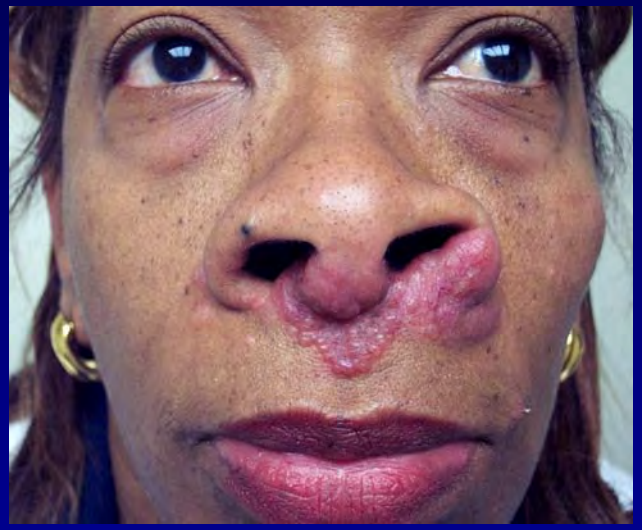
Thalidomide

- *Major Concerns*
- *Not universally available*
- *Inevitable neuropathy with prolonged administration*

  Dermatology: 20-50%
  Symmetric sensorimotor defect
  Peripheral paresthesia
  - *25% recover*
  - *25% improve*
  - *50% unchanged*
- *Teratogenic: exclusions*

Thalidomide

- *Developed severe peripheral mixed motor-sensory neuropathy on 100mg/d*

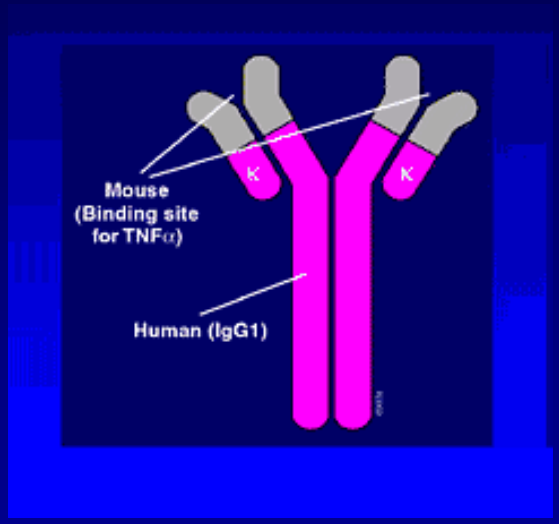


Sarcoidosis Therapy

- *More "Iffy" treatments*
- *Mycophenolate mofetil 2 gr/day*
- *Rituximab*
- *Apremilast*
- *Q-switched ruby laser*
- *Radiotherapy*

Infliximab

- *IV infusion (100mg vial) Dosed by weight*
- *FDA: Crohn's and RA, PsO and PsA, AS*
- *Chimeric antibody against TNF-α*
- *3-10mg/kg/dose*
- *(Usual 5mg/kg)*
- *0, 2 and 6 weeks Then as dictated*



Infliximab

- *Why in sarcoid?*
- *Binding to and inactivating TNF-α, crucial pro-inflammatory cytokine necessary for formation and for maintenance of granuloma*

Infliximab

- *Does it work?*
- *Cutaneous lesions*

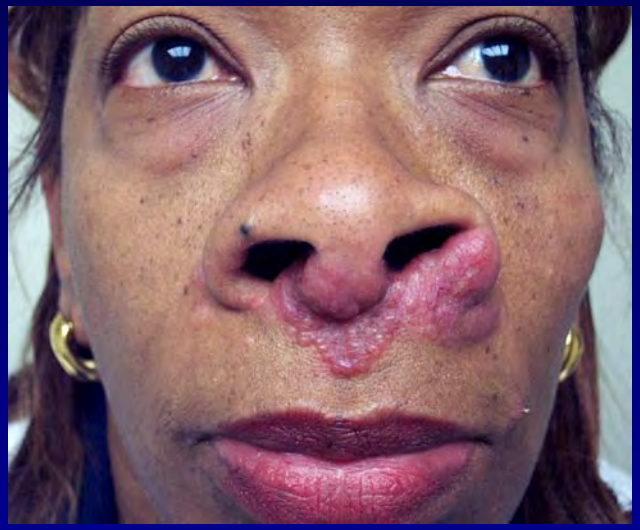
  Sarcoid Vasc Diffuse Lung Dis 18:310, 2001
  J Am Acad Derm 48:290, 2003
  Br J Derm 150:146, 2004
  Sarcoidosis Vasc Diffuse Lung Dis 32:289, 2016
- *Pulmonary disease*

  Sarcoid Vasc Diffuse Lung Dis 18:310, 2001
  J Drugs Dermatol 2:413, 2003 (stabilized)
  Am J Respir Crit Care Med 174: 795, 2006
  Sarcoidosis Vasc Diffuse Lung Dis 23: 201, 2006
- *Multi-organ disease*

  Chest 124:2028, 2003
  Arthritis Rheum 48:3542, 2003
  Respir Med 100: 2053, 2006
  DanMed J 59(12): A4535, 2012
- *Dramatic and rapid response*

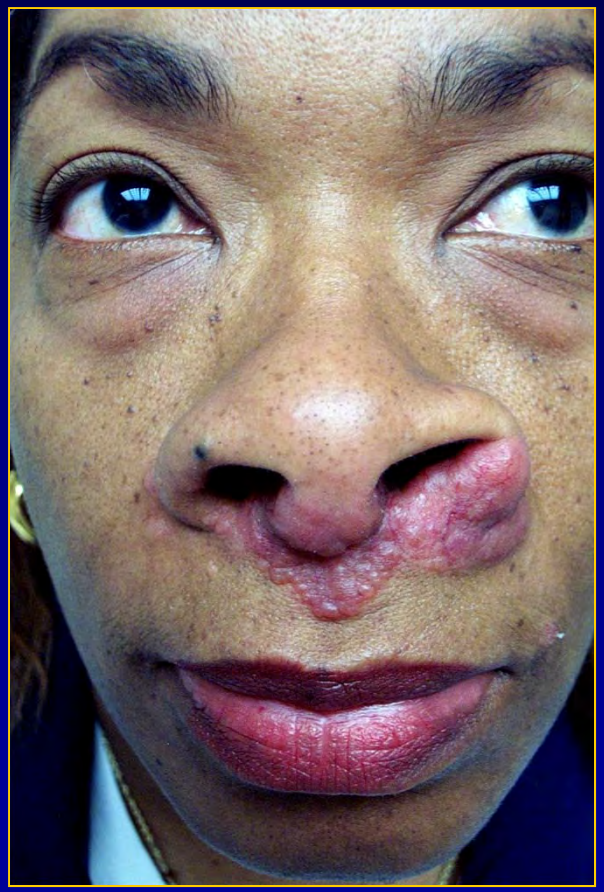
Tetracyclines

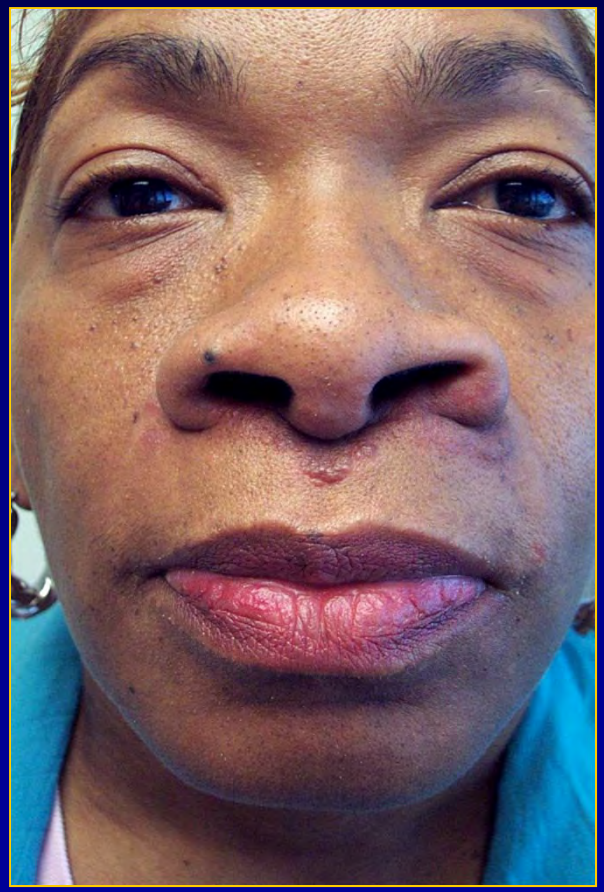
- *Failed steroids*
- *Failed MTX*
- *Failed antimalarials*
- *Failed doxycycline and minocycline*
- *Failed pentoxifylline*
- *Intolerant thalidomide*
- *How about infliximab?*



Sarcoidosis

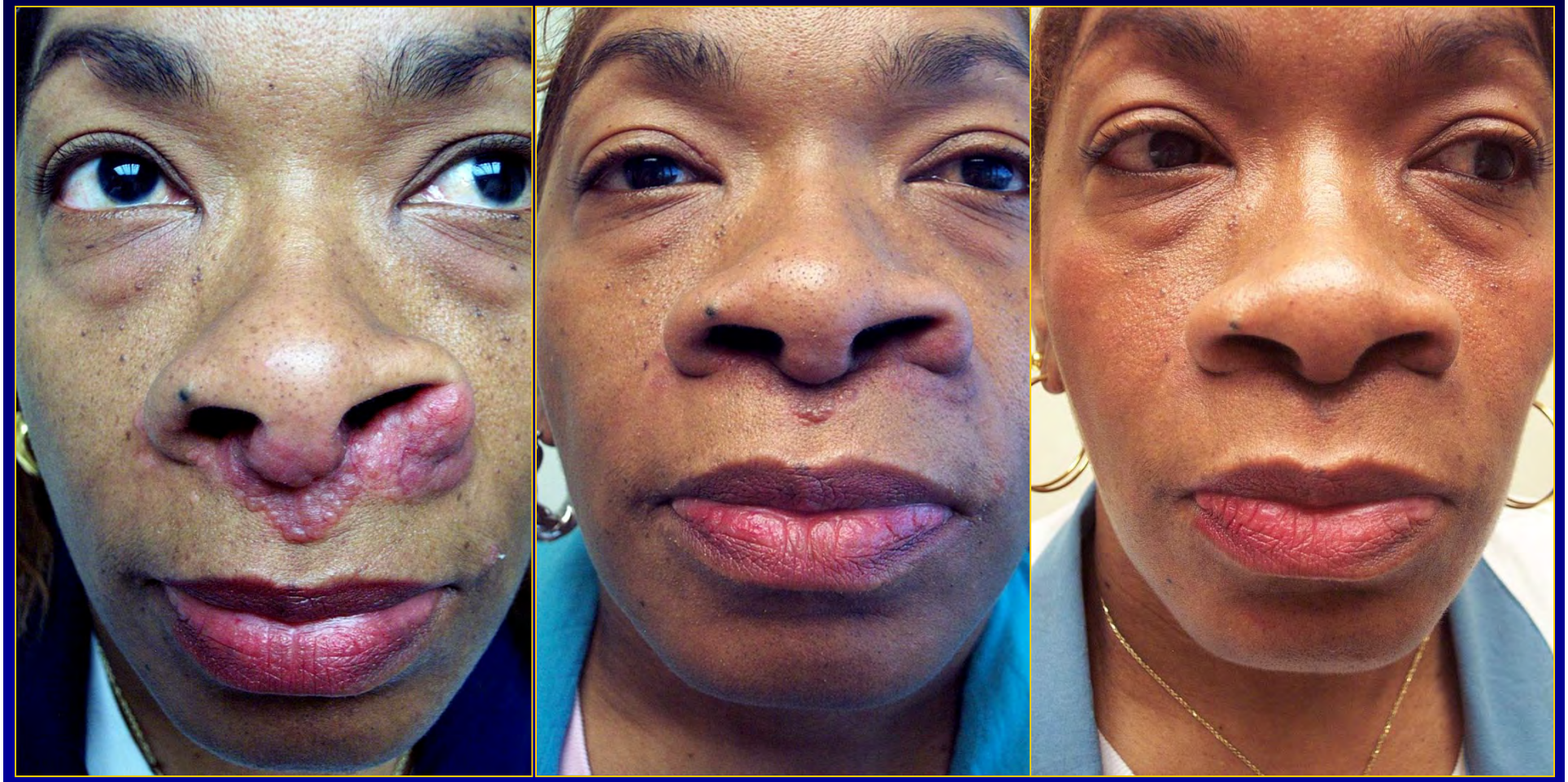
Infliximab 5mg/kg IV x 3 doses (0,2,6 weeks)





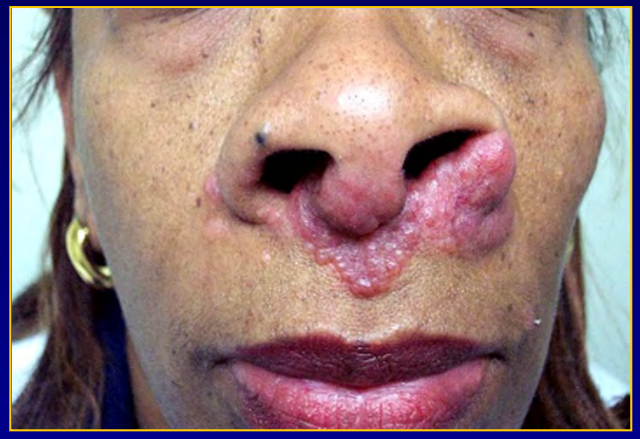
Sarcoidosis

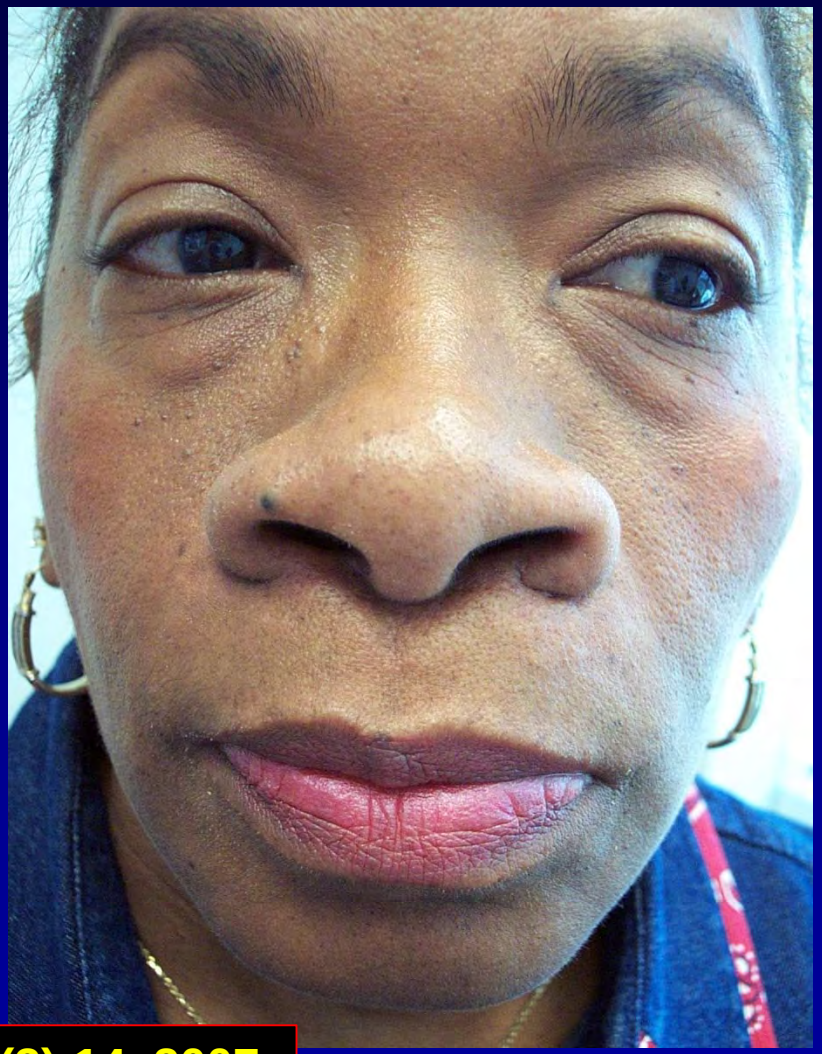
Infliximab 5mg/kg IV x 5 doses (0,2,6,14 and 22 weeks)



Four years later

Infusions Q10 weeks; 5mg/kg





Rosen T: Dermatol Online J 13(3):14, 2007

Infliximab

- *Major Concerns*
- *Long term safety?*
  Induction of lymphoma
- *Increased infection risk?*
  Granulomatous infections such as TB, histo, cocci, crypto, blasto
- *MAKE SURE THAT Dx is SARCOID and NOT TUBERCULOSIS!*
- *Costly: OFF-LABEL*
  Insurance coverage and co-pay???

Adalimumab?

- *Small scale RCT (drug company sponsored)*
- *12 weeks Adalimumab = 10 Placebo = 5*
- *12 week open-label extension (all on drug)*
- *8 week observation (no Rx)*
- *Primary endpoint PGA (total lesional volume)*
- *Responders (PGA ≤ 2)*
  Active: 5/10 (50%) Placebo 1/5 (20%)
- *After 12 more weeks Rx: 10/13 PGA ≤ 2 (77%)*
- *After no Rx: Response rate fell, target lesion volume and surface area increased (ie. Recur)*

J Am Acad Dermatol 2013;68:765-73

Use of Anti-TNF alfa Rx

- *Adalimumab: 80-160mg loading, then 40mg QW (initial and ongoing)*
- *Infliximab: 5mg/kg weeks 0,2,6; then Q4-8 wk*
- *Allow 6 months to assess benefit*
- *Minimum 6-12 months before discontinuation*
- *Tapering: increasing interval between doses*
- *Pre-treatment: TB and HBv and HCv*
- *May use MTX to prevent anti-drug antibody*
- *Pregnancy discouraged*
- *Live vaccines discouraged*
- *Traveling to countries without decent medical and sanitary supplies discouraged*

Sarcoidosis Vasc Diffuse Lung Dis 8;31:91-107, 2014

EUROPEAN RESPIRATORY *journal*
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

CrossMark

Safety and efficacy of ustekinumab or golimumab in patients with chronic sarcoidosis

Marc A. Judson, Robert P. Baughman, Ulrich Costabel, Marjolein Drent, Kevin F. Gibson, Ganesh Raghu, Hidenobu Shigemitsu, Joseph B. Barney, Daniel A. Culver, Nabeel Y. Hamzeh, Marlies S. Wijsenbeek, Carlo Albera, Isham Huizar, Prasheen Agarwal, Carrie Brodmerkel, Rosemary Watt, Elliot S. Barnathan

DOI: 10.1183/09031936.00000914 Published 1 November 2014

Neither at week 16 nor at week 28, was Ustekinumab effective for skin sarcoid

Abstract

Sarcoidosis is characterised by non-caseating granulomas that secrete pro-inflammatory cytokines, including interleukin (IL)-12, IL-23, and tumour necrosis factor (TNF)-α. Ustekinumab and golimumab are monoclonal antibodies that specifically inhibit IL-12/IL-23 and TNF-α, respectively.

Patients with chronic pulmonary sarcoidosis (lung group) and/or skin sarcoidosis (skin group) received either 180 mg ustekinumab at week 0 followed by 90 mg every 8 weeks, 200 mg golimumab at week 0 followed by 100 mg every 4 weeks, or placebo. Patients underwent corticosteroid tapering between weeks 16 and 28. The primary end-point was week 16 change in percentage predicted forced vital capacity (ΔFVC % pred) in the lung group. Major secondary end-points were: week 28 for ΔFVC % pred, 6-min walking distance, St George's Respiratory Questionnaire (lung group), and Skin Physician Global Assessment response (skin group).

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Eur Respir J. 44:1296-30, 2014

Pregnancy

Use in women of child bearing potential

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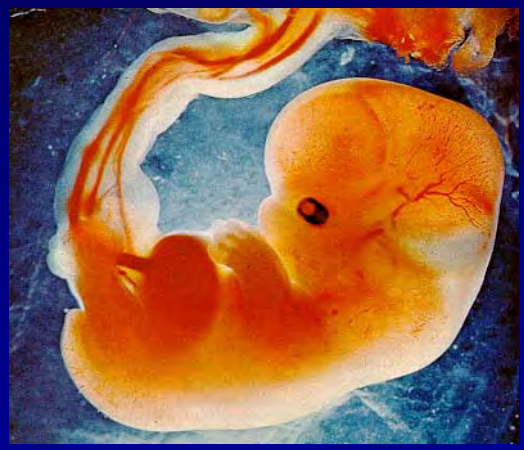
• Isotretinoin	X
• Leflunomide	X
• Thalidomide	X
• Prednisone	D
• Tetracyclines	D
• Pentoxifylline	C
• Antimalarials	C
• Infliximab	B



Pregnancy

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• Isotretinoin	X
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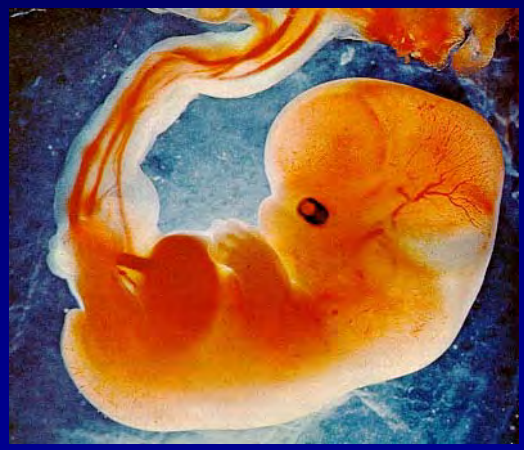

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journal homepage: www.elsevier.com/locate/IJMYCO

Review

Sarcoidosis: Role of non-tuberculosis mycobacteria and *Mycobacterium tuberculosis*

Esmaeil Mortaz [a,b,c], *Ian M. Adcock* [c,*], *Peter J. Barnes* [c]

[a] *Division of Pharmacology and Pathophysiology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Sciences, Utrecht University, Utrecht, The Netherlands*

[b] *Clinical Tuberculosis and Epidemiology Research Center, National Research and Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[c] *Cell and Molecular Biology Group, Airways Disease Section, National Heart and Lung Institute, Imperial College London, Dovehouse Street, London, UK*

Int J Mycobacteriol 3:225-9, 2014

Sarcoid: Novel Rx ("CLEAR")

Original Investigation

Oral Antimycobacterial Therapy in Chronic Cutaneous Sarcoidosis

A Randomized, Single-Masked, Placebo-Controlled Study

Wonder P. Drake, MD; Kyra Oswald-Richter, PhD; Bradley W. Richmond, MD; Joan Isom, LPN; Victoria E. Burke, MD; Holly Algood, PhD; Nicole Braun, PhD; Thyneice Taylor, PhD; Kusum V. Pandit, PhD; Caroline Aboud, BS; Chang Yu, PhD; Naftali Kaminski, MD; Alan S. Boyd, MD; Lloyd E. King, MD, PhD

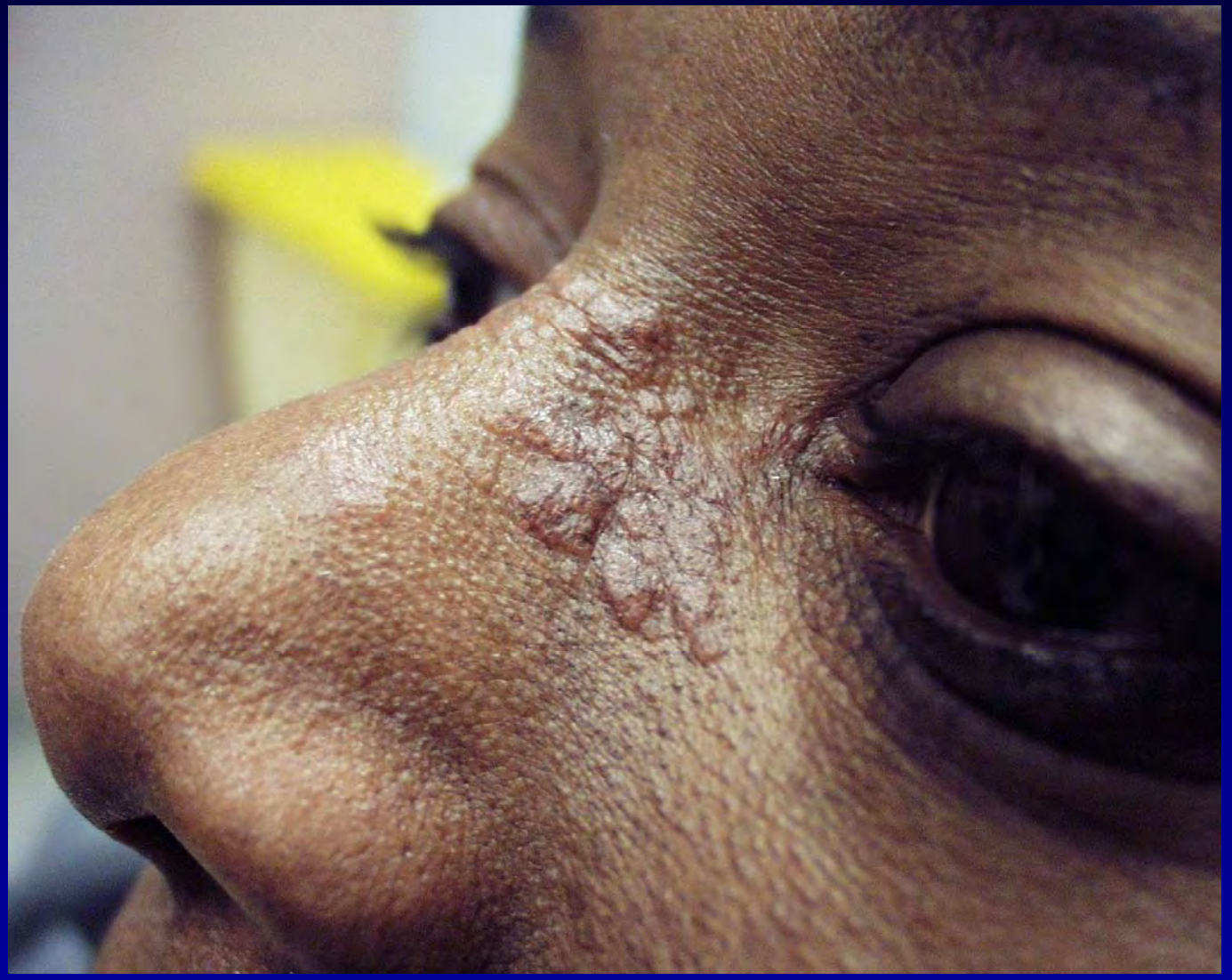
Eight weeks, Active (n=11) versus Placebo (n=11)
Concommitant…..
Levofloxacin 750mg Day 1, then 500mg/d
Ethambutol 25mg/kg/d (maximum 1200mg/d)
Azithromycin 500mg Day 1, then 250mg/d
Rifampin 10mg/kg/d (maximum 300mg/d)
Active had > decrease (vrs increase) in target lesion size and severity

JAMA Dermatol 2013;149:1040-49

Summary

- *Anti-malarials remain first-line therapy for cutaneous sarcoid*
- *Corticosteroids and/or MTX remain next level of therapy*
- *Infliximab appears to offer excellent control, but has risks*
- *Thalidomide data fair, but inevitable problems; RCT failed*
- *Leflunomide promising; toxic*
- *Scant data for isotretinoin, pentoxifylline and tetracyclines*

Thanks for your attention!



Dermatologic Manifestations of Systemic Diseases and Paraneoplastic Syndromes

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Disclosure of Financial Relationships

Julia Nunley, MD

Have no financial relationship with pharmaceutical industry

Am a volunteer Director of the ABD

Do receive an honorarium/royalty for:

Chapters in Medscape eMedicine

Textbook Dermatologic Manifestations of Kidney Disease

Medical Dermatology

MEDICAL DERMATOLOGY SOCIETY

SOCIETY FOR DERMATOLOGY HOSPITALISTS

Goals and Objectives

- Describe the various specific types of cutaneous lupus
- Describe systemic disorders associated with common dermatologic conditions
- Recognize various skin signs of systemic malignancies and paraneoplastic conditions

(Systemic) Lupus Erythematosus

Cutaneous Lupus Subtypes

- Acute lupus
- Subacute lupus erythematosus (SCLE)
- Chronic cutaneous lupus
  - Discoid lupus
  - Tumid lupus
  - Lupus panniculitis
  - Chilblain lupus
- Other miscellaneous
  - Bullous lupus
  - Non-bullous neutrophilic dermatitis
  - Rowell’s syndrome

Acute Lupus

- Photosensitivity reaction
  - Classic “butterfly rash”
    - Reported in 20-60% of patients
    - Typically younger subset
  - Typically transient, but can last for weeks
  - Non-scarring
- Commonly associated with active SLE
  - Complement is usually low

SCLE

- Photosensitivity
  - Also non-scarring
  - Annular and psoriasiform lesions
  - Strong association with SSA / SSB
- May be seen in:
  - SLE (50%)
  - Sjogren’s syndrome
  - C2 deficiency
- 10-20% are drug-induced

Medications associated with SCLE

Antihypertensive agents

- Acebutolol
- Aldactone
- Captopril
- Cilazapril
- Diltiazem
- Nifedipine
- Oxprenolol
- Thiazides
- Verapamil

Antifungal agents

- Griseofulvin
- Terbinafine

NSAIDS

- Naproxen
- Piroxicam

Miscellaneous

- Crysotherapy
- Cinnarizine
- D-penicillamine
- Entanercept
- Interferon beta
- Lansoprazole
- Procainamide
- Ranitidine
- Rifampicin
- Sulfonureas

Drug-Induced SCLE vs Idiopathic

- More commonly wide spread
  - More common to be on LE
- More commonly has bullous features
- EM-like lesions are more common
- More commonly has small vessel vasculitis
- More commonly has malar rash

Marzano AV et al. Br Assoc Dermatol 2011 165:335

Discoid Lupus

- Accounts for 50-85% of cases of cut lupus
  - More common in women; African Americans
  - Most common in 20-40 year olds
  - Photo-activated
    - Mechanism poorly understood
- Scarring cutaneous lesions
  - Can be cosmetically devastating
  - Malignant transformation not rare
- Up to 17% develop SLE

Tumid Lupus

- Non-scarring, photosensitive disorder
- Erythematous, edematous plaques
- Most common on trunk / neck
- Can occur in setting of SLE or stand alone
- Typically few lesions
- Typically highly responsive to antimalarial therapy

Lupus Panniculitis / Profundus

- Rare variant
- Inflammation of the subcutis
- Can be seen with SLE / DLE / independently
- May be a good prognostic indicator in SLE
- May be symptomatic and/or cosmetically destructive
- Lobular panniculitis with lymphocytes and plasma cells

Fraga J. Dermatol Clin 2008

Chilblain's Lupus

- Variant of DLE
  - Acral purplish-blue, tender, chilblain-like nodules and plaques
  - Mainly acral
    - Toes and fingers, heels, calves, knees, nose and ears
  - Related to cold-induced vascular injury
  - Females are predominantly affected
  - ? Associated with smoking
  - Waxes and wanes
  - Difficult to treat

Bullous Lupus

- Rare
- Antibody-mediated subepidermal blistering disorder in a patient with SLE
  - Antibody is to Type VII collagen of BMZ
  - Identical to EBA
- Vesiculo-bullae develop in any distribution
- Dapsone is the treatment of choice

Non-bullous Neutrophilic Dermatitis

- Rare
- Probably under recognized
- Neutrophilic, non-bullous, urticarial eruption in a patient with SLE
  - Mistaken for urticaria, tumid lupus, vasculitis

Systemic Diseases Associated with Cutaneous Conditions

Acanthosis Nigricans

- Familial
- Acquired
  - Insulin resistance
    - Type II diabetes mellitus
    - Polycystic ovary syndrome
      - Hirsutism / acne
  - Adenocarcinoma
    - Stomach

Diabetes Mellitus

- Affects over 29 million Americans (2012)
  - 9.3% of the population
- > 80% are type II diabetics
  - ~30% are undiagnosed
- ~ 30% have skin effects
  - Type I diabetics
    - Autoimmune conditions
  - Type II diabetics
    - Infectious
    - Non- infectious

Non-Infectious Complications

- Acanthosis nigricans
- Necrobiosis lipoidica
- Scleredema
- Diabetic dermopathy
- Granuloma annulare

Necrobiosis Lipoidica

- An unusual and uncommon granulomatous inflammatory disease of the skin
- Most commonly found on bilaterally on the shins

Necrobiosis Lipoidica

- Occurs in 0.3% of diabetics
  - No association with glycemic control
- 2/3 have diabetes
  - Many have FH diabetes
- 3-5 times more common in women

Scleredema

- Non-pitting induration
  - Affects type I and type II DM
  - Incidence is between 12-50% of patients
- Due to excessive mucin deposition between thickened bundles of collagen
- May affect arms/ hand
  - Finger / joint findings frequently co-exist

Scleredema – consider other causes

- Diabetes mellitus (type 3)
- Antecedent infection (type 1)
  - *Streptococcal* infection
- Blood dyscrasia (type 2)
  - Paraproteinemia / myeloma
- Other / rare
  - Hyperparathyroidism
  - Rheumatoid arthritis and Sjögren syndrome
  - HIV and AIDS–related
  - Malignant insulinoma; Carcinoid

Scleredema

- Work up for new onset:
  - ASO or streptozyme
  - Blood glucose level(s)
  - Serum immunofixation
    - IgG kappa

Diabetic Dermopathy

- Occurs in up to 40%
  (9-55% range)
  - M>F – 2:1
  - More common in older patients
  - More common with longer duration of diabetes
  - Not related to glycemic control (Hgb A1C)

Diabetic Dermopathy

- Marker for diabetes
- Most significant marker for complications:
  - Microangioprocesses:
    - Nephropathy
    - Neuropathy
    - Retinopathy
  - Large vessel complications:
    - Coronary artery disease – 53% in one study

Granuloma Annulare

- Exact cause unknown
  - ? Cell-mediated hypersensitivity reaction
- Multiple systemic associations
  - Diabetes mellitus
  - Thyroid disease
  - Malignancy
  - Other
    - Dyslipidemia
    - Infection – HIV, HCV, HBV
    - Drug-induced
- May depend on clinical presentation

Granuloma Annulare

- Classic localized variant
- Generalized annular variant
- Rare variants
  - Subcutaneous, macular/patch
- Atypical variants
  - Perforating form
  - Photosensitive
  - Palmar, mucosal
  - Disseminated papular

GA and Thyroid Disease

- Associated with localized / generalized GA
  - Uniformly women
  - Age 20-75 years
- Various case series - 6-13% have thyroid disease NOS
- Case series - 12% with autoimmune thyroiditis (Vasquez-Lopez JAAD 2003;517-20)
  - Supports the theory of immune based pathogenesis

GA and Malignancy

- Usually older patients
- Usually atypical GA
- Hematologic are more common (>50%)
  - Hodgkin's and non-Hodgkin's lymphomas
  - Leukemias
- Solid tumors have been reported
  - Lung, breast, cervical, colon, prostate, testicles, thyroid

From: **Dyslipidemia in Granuloma Annulare: A Case-Control Study**

Arch Dermatol. 2012;148(10):1131-1136.
doi:10.1001/archdermatol.2012.1381

Variable	GA Cases (n = 140)	Controls (n = 420)	*P* Value[b]
Age, mean (SD), y	50.1 (13.4)	49.9 (13.5)	.91
Median (range)	50.5 (19-81)	51.0 (18-84)	.95
Female sex	[illegible]	309 (73.6)	>.99
White race	135 (96.4)	405 [illegible]	>.99
Socioeconomic status			
Low	35 (25.0)	107 (25.5)	
Intermediate	20 (14.3)	92 (21.9)	.11
High	85 (60.7)	221 (52.6)	
Total cholesterol level, mean (SD), mg/dL	213.6 (38.9)	190.1 (34.6)	**<.001**
Hypercholesterolemia	92 (65.7)	133 (31.7)	**<.001**
LDL-C level, mean (SD), mg/dL	127.1 (38.3)	113.6 (30.0)	**<.001**
High LDL-C	64 (45.7)	102 (24.3)	**<.001**
Triglyceride concentration, mean (SD), mg/dL	147.7 (81.6)	118.1 (68.0)	**<.001**
Hypertriglyceridemia	52 (37.1)	96 (22.8)	**<.001**
HDL-C level, mean (SD), mg/dL	55.7 (24.4)	52.4 (15.6)	.06
Low HDL-C	32 (22.9)	78 (18.6)	.27
Dyslipidemia	111 (79.3)	218 (51.9)	**<.001**
Comorbidities			
Type 2 diabetes mellitus	22 (15.7)	68 (16.2)	.89
Hypertension	46 (32.8)	145 (34.5)	.71
Hypothyroidism	16 (11.4)	50 (11.9)	.87
Obesity	51 (36.4)	148 (35.2)	.79
Metabolic syndrome	32 (22.9)	77 (18.3)	.26
Current smoker	[illegible]	54 (12.8)	.09
β-Blocker use	18 (12.8)	39 (9.3)	.22

GA and Dyslipidemia

- 4 fold greater odds of dyslipidemia
- More common in generalized annular GA
  - Compared to localized or atypical forms
- ? Associated with chronic inflammatory state

Wu. Arch Dermatol 2012;148:1131-6

Laboratory Evaluation of GA

- TSH / free thyroxine
- Complete blood count with differential
- Lipid panel
- Age appropriate cancer screening
  - Women – mammo; pelvic with PAP, colonoscopy
  - Men – PSA, colonoscopy
- HIV / HCV / HBV*
- Imaging studies
  - CXR / CTs *

Psoriasis - Associations

- 73% of patients have at least 1 comorbidity
  - Metabolic syndrome
    - Obesity, HTN, DM, CVD
  - Inflammatory bowel disease
  - Uveitis
  - Psychiatric disturbances
- Common link is likely systemic inflammation

Psoriasis – possible associations

- Osteoporosis / osteopenia
- COPD

Psoriasis – Osteopenia / Osteoporosis?

- Pathogenesis involves similar cytokines
  - IFN-gamma; IL-6; TNF-alpha
  - Suggests more susceptibility for patients
- Drug therapy may predispose
- Joint immobilization with PsA may predispose
- Conflicting data
  - More complicated in patients with PsA
  - More common in long term psoriasis
  - May be more prevalent in men

Psoriasis – COPD?

- Simply a fact of common risk factors ???
  - Obesity
  - Smoking
  - Metabolic syndrome
- Case-controlled study:

  (Drieher. Br J Dermatol 2008;158:956-60)
  - COPD found in 5.7% in psoriasis vs 3.6% ($p<0.001$)

Psoriasis and Healthy Life Style

- To reduce comorbidities
  - Cardiovascular
  - Bone metabolism
  - Pulmonary
- Recommendations
  - Diet
  - Exercise
  - No smoking

Xanthalasma Palpebrarum (XanP)

- Planar xanthomas of inner canthi
  - 50% associated with hyperlipidemia

XanP - Association

Esmat S. Clin Exp Dermatol 2015;40:373
Akyuz AR, Wein Klin Wochenschr ePub March 2016
Cohen YK et al. Dermatol Pract Concept 2015;5(4):16

- Atherosclerosis
  - Not all related to hyperlidemia
  - (+) Markers of premature atherosclerosis
    - Increased risk for myocardial infarction/ stroke
    - Increased risk for PAD
- Increased risk for NASH
- Need more than lipid screening to evaluate cardiovascular risks

XanP - Associations

- Primary biliary cirrhosis
  - Second most common skin finding
    - After pruritus
    - More common in PBC than any other cholestatic liver disease
  - Inconsistently associated with hyperlipidemia
  - May regress as disease progresses

Alopecia Areata

- Common
- Non-scarring, immune-mediated, type of alopecia

Alopecia Areata and Other Diseases

Autoimmune disorder	Incidence in AA, %	Reference
Vitiligo	1.8–7.0	15,16,33,46,47
Thyroid disorder	2.3–14.6	16,33,34,46
Irritable bowel syndrome	2.0	46
Psoriasis ± psoriatic arthritis	1.9–6.3	34,46
Systemic lupus erythematosus	1.5	34
Rheumatoid arthritis	0.9–3.9	19,34,46
Diabetes mellitus	0.4–11.1	15,46

Alopecia Areata - Associations

- 584 AA patients vs control
- Associated conditions:
  - Atopic conditions (rhinitis and eczema*)
  - Thyroid disease*
  - Anxiety / depression
  - Vitamin D deficiency*
  - Anemia*
  - Celiac
- Statistical Increased incidence in *

Miller R. jidonline 2015;17:61-62

Alopecia Areata and Zinc

- Essential trace element – affects many aspects of metabolism
- May impact hair biology
  - Immunomodulatory effects
  - Functional activities of the hair follicle
- Decreased zinc levels found in AA
  - 15/44 patients with low zinc
  - 9/15 showed (+) therapeutic effects with replacement – but not statistically significant

(Park et al Ann Derm 2009; 21;142-146)

Alopecia Areata and Zinc

Fattah et al. 2016 study:

- Zinc level significantly lower in pts with AA
- Inverse correlation between zinc level and: AA severity, disease duration, resistance
- Conclusion:
  - Low zinc levels were a marker of severity, etc
  - Supplementation may be therapeutic

Fattah et al. Int Dermatol 2016;55:24-9

Necrolytic Acral Erythema

- Pruritic hyperkeratotic rash affecting acral sites
- Associations
  - Hepatitis C viral infection
  - Zinc deficiency
  - Metabolic syndrome ??

Skin Findings in Systemic Malignancies

Skin Findings in Systemic Malignancies

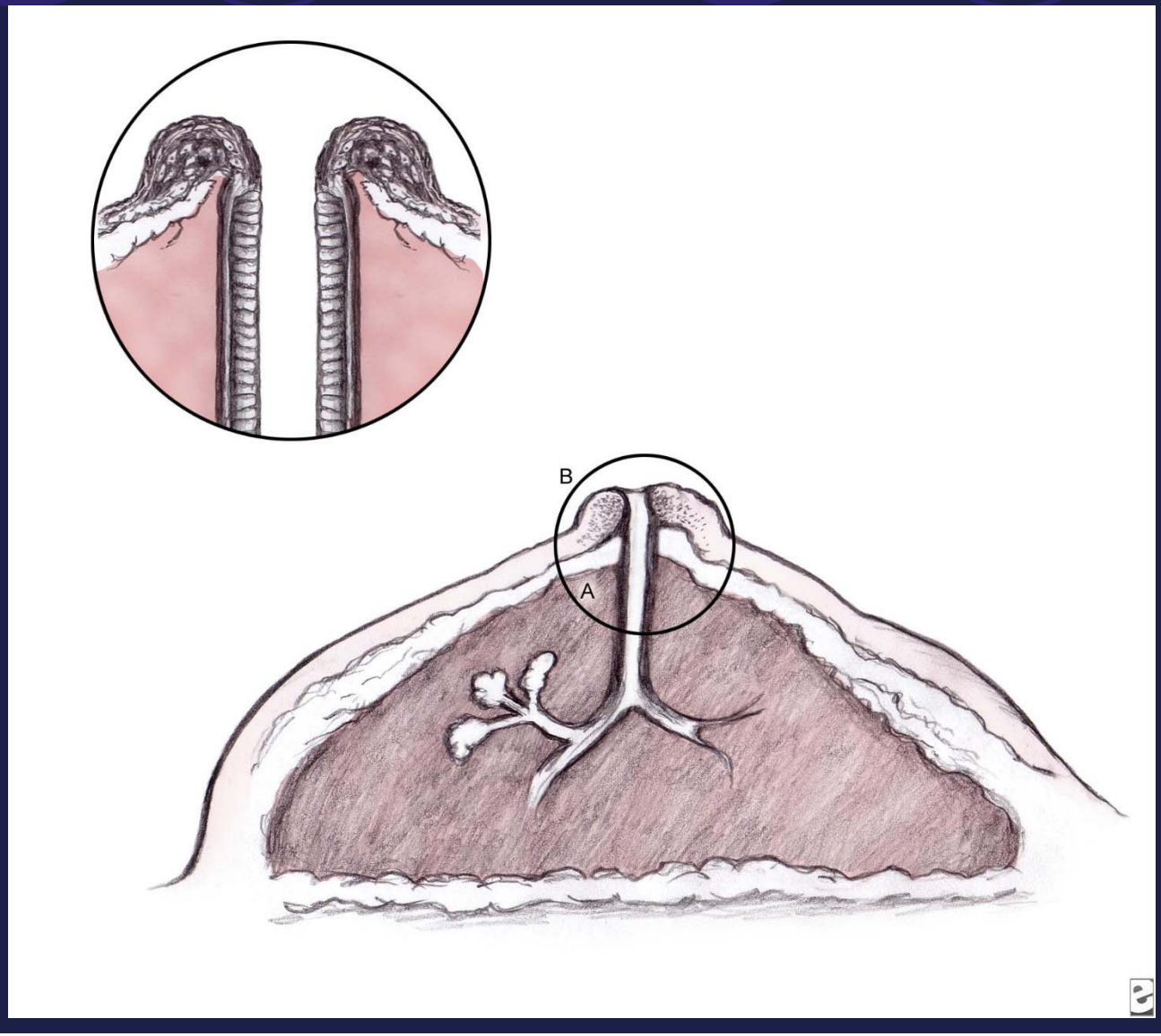
- Associated with paraproteinemia
- Cutaneous metastatic disease
- Paraneoplastic syndromes

Skin Disorders with Paraproteinemia

- Scleredema
- Scleromyxedema
- Necrolytic xanthogranuloma
- Pyoderma gangrenosum
- Erythema elevatum diutinum
- Systemic amyloidosis

Cutaneous Metastatic Lesions

Paget's Disease of the Breast



Paraneoplastic Syndromes

Paraneoplastic Syndromes

- Acanthosis nigricans
- Acquired ichthyosis
- Bazex syndrome
- Extramammary Paget's
- Florid cutaneous papillomatosis
- Acquired diffuse palmoplantar keratoderma
- Pityriasis rotunda
- Sign of Leser Tre'lat
- Tripe palms
- Dermatomyositis
- Erythema gyratum repens
- Hypertrophic osteoarthropathy
- Multicentric reticulohistocytosis
- Necrolytic migratory erythema
- Sweet syndrome
- Paraneoplastic pempigus
- Carcinoid syndrome
- Hypertrichosis lanuginosa acquisita
- Trousseau syndrome
- Subacute cutaneous lupus

Nguyen. eMedicine.medscape.com

Paraneoplastic Pemphigus

- First described in 1990
- Autoimmune mucocutaneous blistering disease
  - Stomatitis (refractory) most common
- Most commonly associated with lymphoproliferative disorders
  - Most common non-Hodgkin's lymphoma
- 90% mortality rate
  - Usually due to pulmonary disease

Dermatomyositis

- Risk of malignancy is ~ 25%
- Adenocarcinomas more common
  - Ovarian, lung, breast, pancreatic, colon, prostate
- Malignancy may precede / occur concomitantly / or follow
  - 2-3years
- Cancer screening is indicated

Femia AN. Am J Clin Derm 2013; June

Nail Fold Telangiectasia

- Dermatomyositis
- Systemic lupus erythematosus
- Scleroderma
- Rheumatoid arthritis

Dermatomyositis vs SLE

- Photosensitivity
  - “Shawl” distribution
- Heliotrope rash
- Nail fold telangiectasia
- (+) ANA
- Erythema over joints
- Muscle weakness / enzyme abnormalities
- Gottron’s papules
- Paraneoplastic

- Photosensitivity
  - Butterfly rash
- Heliotrope rash
- Nail fold telangiectasia
- (+) ANA
- Erythema between joints
- Anemia … etc
- DLE /SCLE / vasculitis
- Cardiovascular disease

Sweet Syndrome
(Acute febrile neutrophilic dermatosis)

- Acute onset of fever and erythematous papules or plaques
- Associated with infections, IBD, malignancy, drugs, autoimmune disease
  - May be idiopathic or associated with pregnancy
- Most common malignancy is AML

Raza. Int J Oncol 2013

Case

- 74 yo referred in for rash
- Sudden onset of rash and headache about 4 weeks earlier –
  - Negative head MRI
- Headache persisted; now unstable with slurred speech and disoriented
- On her way to clinic she became transiently unconscious

Case

- Oriented x 3
- Unstable gait – in wheel chair
- Symmetric facial expressions
- Rash
  - SCLE
- SIADH associated with small cell carcinoma

SCLE as a Paraneoplastic Sign

- First reported in 1986 with breast cancer
- Since then ~ 10 have been reported
- Associated cancers:
  - Breast
  - Lung – mostly small cell lung cancer some NOS

Neumann et al. Dermatologica 1986;173(3)
Schewach et al. JAAD 1988;19(2 pt 2)
Brenner et al. Dermatol 1997;194
Renner et al. Eur J Dermatol 2008;18(6)

Conclusions

- Recognize the various skin signs of lupus
- Screen patients with common dermatologic conditions for associated systemic disorders
- Recognize some important skin signs of systemic malignancies