Optometric Education Consultants

Oral Pharmaceuticals in Eye Care

"Pearls from an Optometrist and Pharmacist "

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Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- Lectured for: Alcon, Allergan, Aerie, B&L, BioTissue, Kala, Maculogix, Optovue, RVL, Heru, Santen
  - Disclosure: Receive speaker honorariums
- Advisory Board: Allergan, Alcon, Dompe, Eyenovia Tarsus, Visus
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
  - Disclosure: Non-salaried financial affiliation with Pharmanex
- Envolve: PA Medical Director, Credential Committee
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
- The content of this activity was prepared independently by me - Dr. Caldwell
- The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service
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Disclosures: Tracy Offerdahl, PharmD

All relevant relationships have been mitigated

- Dr. Offerdahl has the following financial disclosure:
  - Boiron: honorarium, webinar/speaker
- Has not received any assistance from any commercial interest in the development of this course

Text me your comments and questions

814-931-2030

Greg Caldwell, OD, FAAO

Your favor drink?

Oral Pharmaceuticals in Eye Care
Agenda

- FDA Pregnancy Categories
  - Pre-June 30, 2015
  - Post-June 30, 2015
- Antibiotics
  - Anti-infectives
  - Anti-inflammatory
- Antivirals
  - Anti-infectives
- How to apply them in patient care
- Pitfalls to avoid
- Increase confidence when selecting an oral antibiotic or antiviral

FDA Pregnancy Categories

- Category A- studies in pregnant women…no risk
- Category B- animal studies no risk but human not adequate…or…animal toxicity but human studies no risk…safe
- Category C- animal studies show toxicity human studies inadequate, but benefit of use may exceed risk…OR…there are no adequate studies in animals or humans…avoid (MOST new drugs are here)
- Category D- evidence of human risk but benefits may outweigh risks…avoid
- Category X- fetal abnormalities, risk>benefits…avoid

Pregnancy and Lactation Labeling Rule-FDA

December 4, 2014, Final Rule

- **Effective June 30, 2015**
  - Effective now for new medications and a 3–5-year phase in period (application)
- Labeling for human prescription drugs and biological products will include:
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential
- Pregnancy (8.1)
  - Pregnancy Exposure Registry – omit if not applicable
  - Risk Summary – required subheading
  - Clinical Considerations- omit if none of the headings are applicable
    - Disease-associated maternal and/or embryo/fetal risk- omit if not applicable
    - Dose adjustments during pregnancy and the postpartum period - omit if not applicable
    - Maternal adverse reactions - omit if not applicable
    - Fetal/Neonatal adverse reactions- omit if not applicable
    - Labor or delivery - omit if not applicable
  - Data- omit if none of the headings are applicable
    - Human Data - omit if not applicable
    - Animal Data- omit if not applicable

Pregnancy and Lactation Labeling Rule-FDA

December 4, 2014, Final Rule

- Lactation (8.2)
  - Risk Summary- required subheading
  - Clinical Considerations– omit if not applicable
  - Data– omit if not applicable
- Females and Males of Reproductive Potential (8.3) - omit if none of the headings are applicable
  - Pregnancy testing– omit if not applicable
  - Contraception– omit if not applicable
  - Infertility – omit if not applicable

Pre-June 30, 2015

respectively, revealed no evidence of teratogenicity.

8.3 Nursing Mothers

Following oral administration of a 500 mg dose of VALTREX to 5 nursing mothers, peak acyclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 times (median 1.4) the corresponding maternal acyclovir serum concentrations. The acyclovir breast milk AUC ranged from 1.4 to 2.6 times (median 2.2) maternal serum AUC. A 500 mg maternal dosage of VALTREX twice daily would provide a nursing infant with an oral acyclovir dosage of approximately 0.6 mg/kg/day. This would result in less than 2% of the exposure obtained after administration of a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir to the nursing infant. Unchanged valacyclovir was not detected in maternal serum, breast milk, or infant urine. Caution should be exercised when VALTREX is administered to a nursing woman.

8.4 Pediatric Use

VALTREX is indicated for treatment of cold sores in pediatric patients ≥12 years of age and for treatment of chickenpox in pediatric patients 2 to <18 years of age *[see Indications and Usage (1.2), Dosage and Administration (2.2)]*.

The use of VALTREX for treatment of cold sores is based on 2 double-blind, placebo-controlled clinical trials in healthy adults and adolescents (≥12 years of age) with a history of recurrent cold sores *[see Clinical Studies (14.1)]*.

The use of VALTREX for treatment of chickenpox in pediatric patients 2 to <18 years of age is based on single-dose pharmacokinetic and multiple-dose safety data from an open-label trial with valacyclovir and supported by efficacy and safety data from 3 randomized, double-blind, placebo-controlled trials evaluating oral acyclovir in pediatric patients with chickenpox *[see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)]*.

The efficacy and safety of valacyclovir have not been established in pediatric patients:

- <12 years of age with cold sores
- <18 years of age with genital herpes
- <18 years of age with herpes zoster
- <2 years of age with chickenpox
- for suppressive therapy following neonatal HSV infection.

The pharmacokinetic profile and safety of valacyclovir oral suspension in children <12 years of age were studied in 3 open-label studies. No efficacy evaluations were conducted in any of the 3 studies.

Study 1 was a single-dose pharmacokinetic, multiple-dose safety study in 27 pediatric patients 1 to <12 years of age with clinically suspected varicella-zoster virus (VZV) infection *[see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)]*.

Study 2 was a single-dose pharmacokinetic and safety study in pediatric patients 1 month to <6 years of age who had an active herpes virus infection or who were at risk for herpes virus infection. Fifty-seven subjects were enrolled and received a single dose of 25 mg/kg valacyclovir

In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of VALTREX. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to VALTREX.

General: Facial edema, hypertension, tachycardia.

Allergic: Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritus, rash, and urticaria *[see Contraindications (4)]*.

CNS Symptoms: Aggressive behavior, agitation, ataxia, coma, confusion, decreased consciousness, dysarthria, encephalopathy, mania, and psychosis, including auditory and visual hallucinations, seizures, tremors *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), (8.6)]*.

Eye: Visual abnormalities.

Gastrointestinal: Diarrhea.

Hepatobiliary Tract and Pancreas: Liver enzyme abnormalities, hepatitis.

Renal: Renal failure, renal pain (may be associated with renal failure) *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), (8.6)]*.

Hematologic: Thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis, TTP/HUS *[see Warnings and Precautions (5.1)]*.

Skin: Erythema multiforme, rashes including photosensitivity, alopecia.

7 DRUG INTERACTIONS

No clinically significant drug-drug or drug-food interactions with VALTREX are known *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

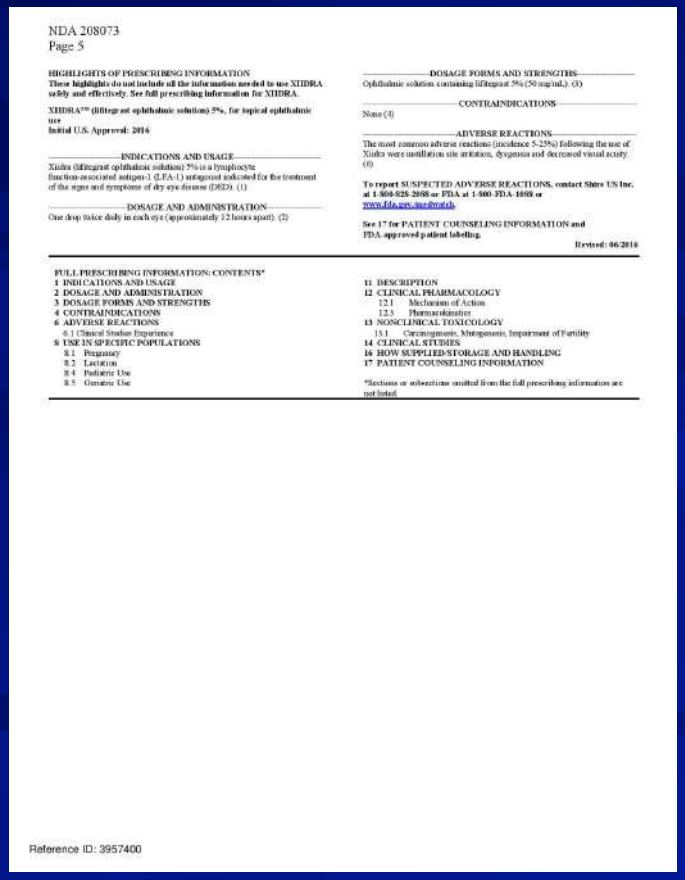
8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of VALTREX or acyclovir in pregnant women. Based on prospective pregnancy registry data on 749 pregnancies, the overall rate of birth defects in infants exposed to acyclovir in-utero appears similar to the rate for infants in the general population. VALTREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses.

Animal reproduction studies performed at oral doses that provided up to 10 and 7 times the human plasma levels during the period of major organogenesis in rats and rabbits,

Post-June 30, 2015



NDA 208073
Page 5

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XIIDRA safely and effectively. See full prescribing information for XIIDRA.

XIIDRA™ (lifitegrast ophthalmic solution) 5%, for topical ophthalmic use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE
Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED). (1)

DOSAGE AND ADMINISTRATION
One drop twice daily in each eye (approximately 12 hours apart). (2)

DOSAGE FORMS AND STRENGTHS
Ophthalmic solution containing lifitegrast 5% (50 mg/mL). (3)

CONTRAINDICATIONS
None (4)

ADVERSE REACTIONS
The most common adverse reactions (incidence 5-25%) following the use of Xiidra were instillation site irritation, dysgeusia and decreased visual acuity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3957400

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation Day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3)]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from pre-mating through gestation Day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing five, 400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation Days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

11 DESCRIPTION

The chemical name for lifitegrast is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. The molecular formula of lifitegrast is $C_{29}H_{24}Cl_2N_2O_7S$ and its molecular weight is 615.5 g/mol. The structural formula of lifitegrast is:

Post-June 30, 2015

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use UPNEEQ safely and effectively. See full prescribing information for UPNEEQ.

UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), 0.1%, for topical ophthalmic use
Initial U.S. Approval: 1964

----------INDICATIONS AND USAGE----------
UPNEEQ is indicated for the treatment of acquired blepharoptosis in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop into one or both ptotic eye(s) once daily. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution, 0.1% oxymetazoline as salt, equivalent to 0.09% oxymetazoline as base

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Alpha-adrenergic agonists as a class may impact blood pressure. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens. (5.1)
- Use with caution in patients with cerebral or coronary insufficiency or Sjogren's syndrome and advise patients to seek medical care if signs and symptoms of potentiation of vascular insufficiency develop. (5.2)
- Advise patients to seek immediate medical care if pain, redness, blurred vision and photophobia occur (signs and symptoms of acute angle closure). (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence 1-5%) are: punctate keratitis, conjunctival hyperemia, dry eye, vision blurred, instillation site pain, eye irritation and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact RVL Pharmaceuticals, Inc. at 1-877-482-3788 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no available data on UPNEEQ use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 7 and 278 times the maximum recommended human ophthalmic dose (MRHOD), respectively, based on dose comparison. *[see Data]*. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Animal Data
Effects on embryo-fetal development were evaluated in rats and rabbits following oral administration of oxymetazoline hydrochloride during the period of organogenesis. Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 0.2 mg/kg/day in pregnant rats during the period of organogenesis (28 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 1 mg/kg/day in pregnant rabbits during the period of organogenesis (278 times the MRHOD, on a dose comparison basis).

Reference ID: 4637843

Maternal toxicity, including decreased maternal body weight, was produced at the high dose of 1 mg/kg/day in pregnant rabbits and was associated with findings of delayed skeletal ossification.

In a rat prenatal and postnatal development study, oxymetazoline hydrochloride was orally administered to pregnant rats once daily from gestation day 6 through lactation day 20. Maternal toxicity was produced at the high dose of 0.2 mg/kg/day (28 times the MRHOD, on a dose comparison basis) in pregnant rats and was associated with an increase in pup mortality and reduced pup body weights. Delayed sexual maturation was noted at 0.1 mg/kg/day (14 times the MRHOD on a dose comparison basis). Oxymetazoline hydrochloride did not have any adverse effects on fetal development at a dose of 0.05 mg/kg/day (7 times the MRHOD, on a dose comparison basis).

8.2 Lactation
Risk Summary
No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breastmilk production, or to establish the level of oxymetazoline present in human breastmilk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for UPNEEQ and any potential adverse effects on the breastfed child from UPNEEQ.

8.4 Pediatric Use
Safety and effectiveness of UPNEEQ have not been established in pediatric patients under 13 years of age.

Dacryocystitis

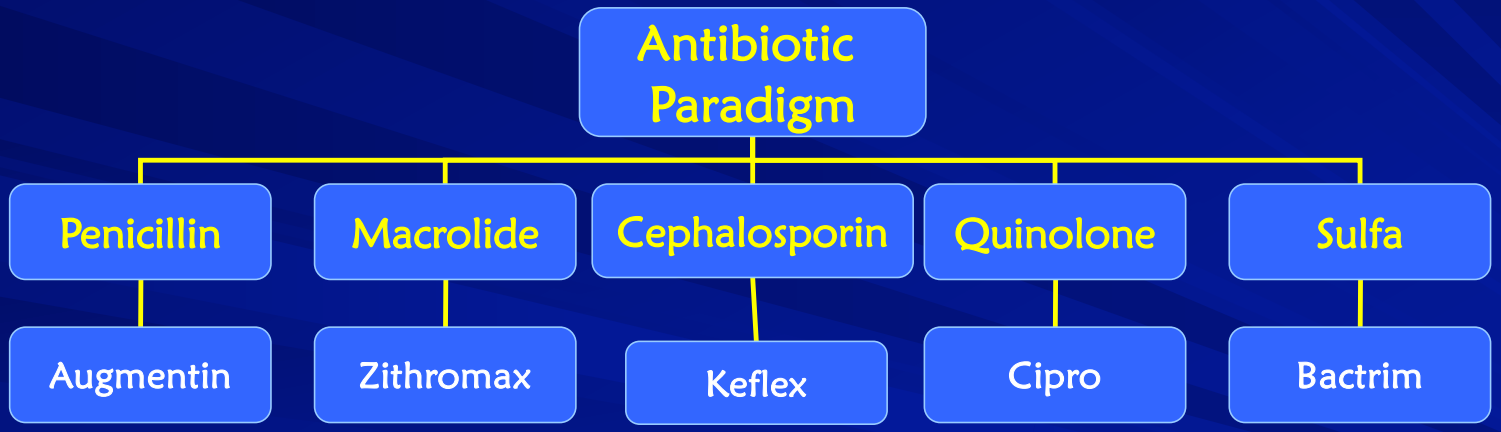
Text me your answer 814-931-2030

Patient as a severe allergic reaction to Penicillin and Keflex (Epipen)

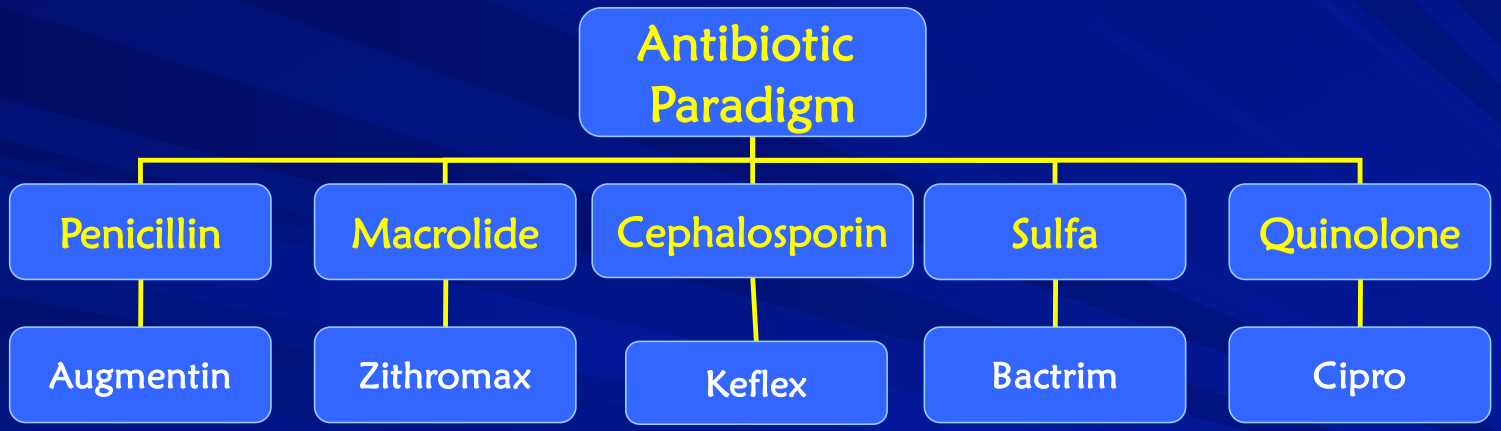
Which antibiotic would you use?

A. Augmentin
B. Azithromycin
C. Cephalexin
D. Bactrim
E. Cipro

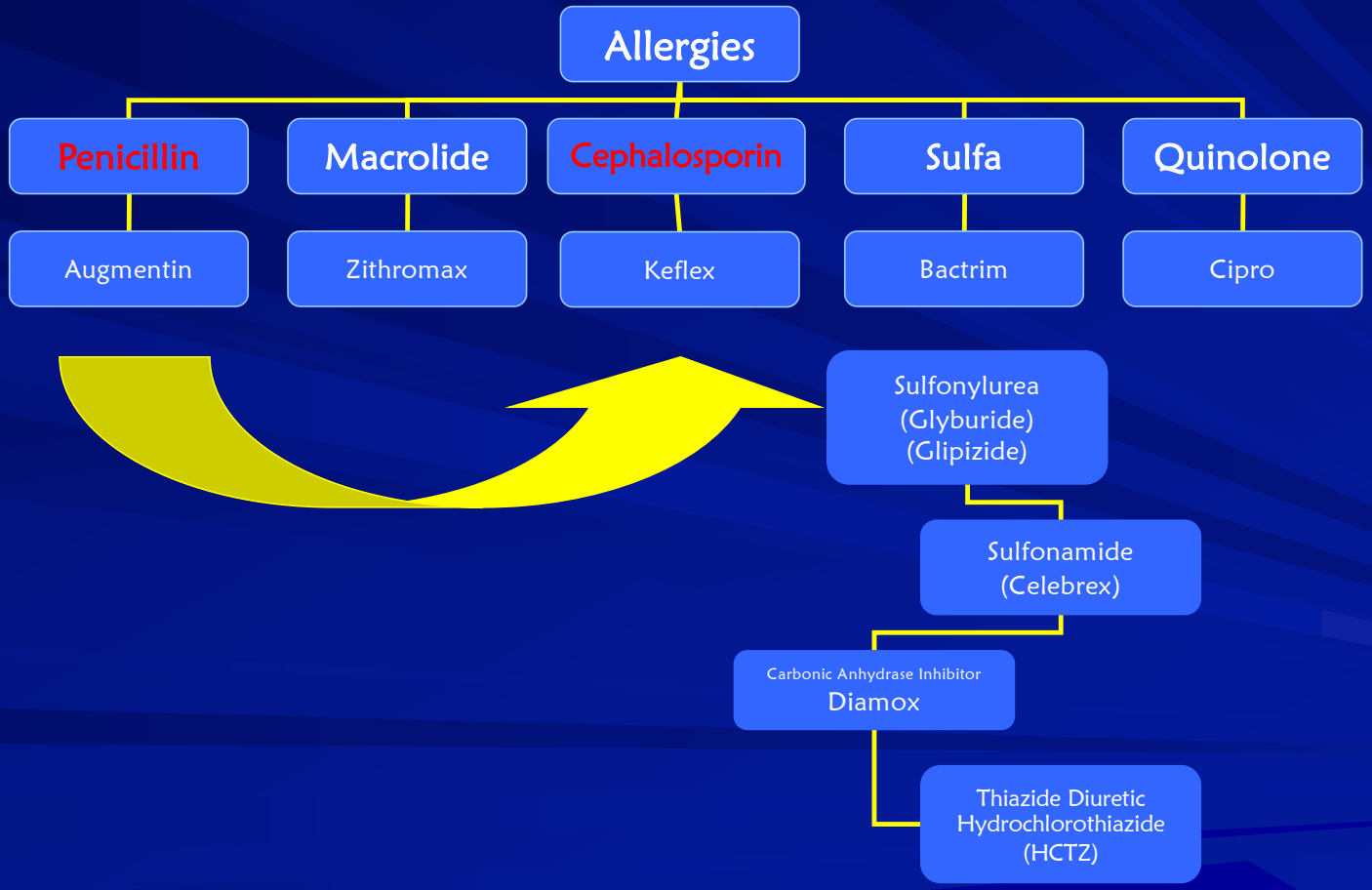
Antibiotic Paradigm Thru 2019



Antibiotic Paradigm Changed 2020

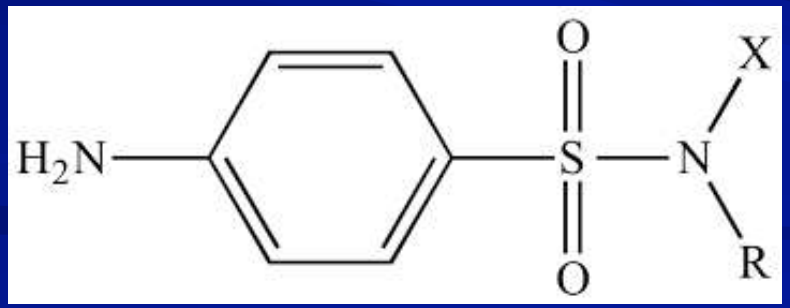


Cross Reaction



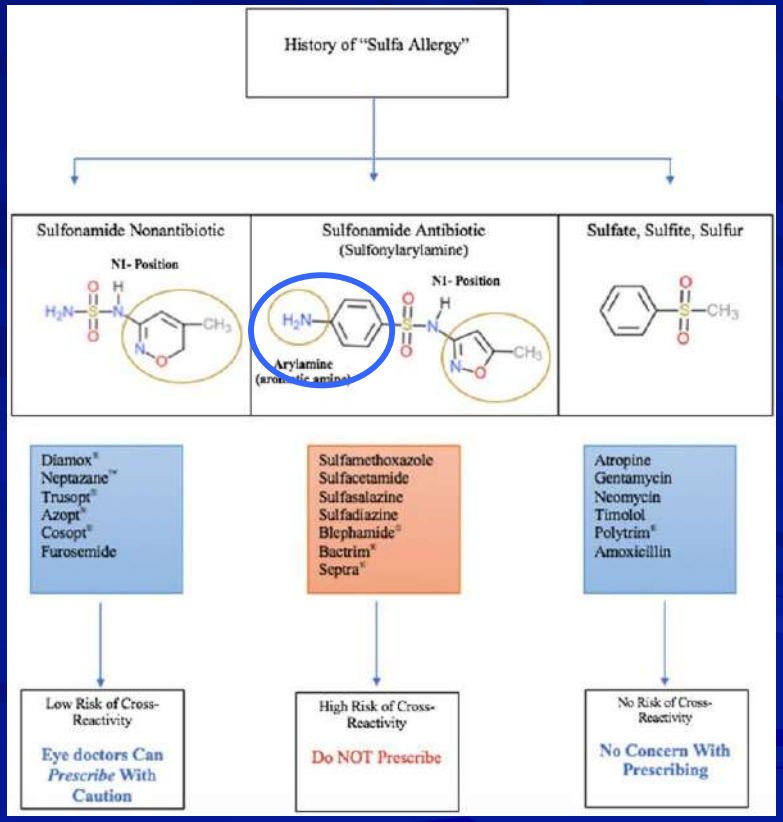
"Sulfa Antibiotic Allergy"

- If a true allergy: Mast cell and Ige mediated, causing hives, itch, congestion, lip and tongue swelling, tightness in throat, and bronchial constriction
  - ✶ Anaphylaxis
- The "S" is typically not the hapten/antigen
- The arylamine group is the hapten/antigen



What to ask about allergies

- For the patient
  - ★ When did you react?
  - ★ What was the reaction?
    - Systemic versus topical
- For you…
  - ★ For sulfa allergic patients
    - Antibiotic structure sulfa allergy
      - Sulfamethoxazole/trimethoprim
    - Non-antibiotic structure agents
      - Carbonic anhydrase inhibitors
      - Hydrochlorothiazide
      - Celecoxib (Celebrex)
      - Glipizide, glyburide, glimepiride



Amoxicillin + Clavulanic acid (Augmentin)

- "*Uber Amoxicillin*"
- Kills everything, good for everyone
  - 12 weeks old and older
- Safe in pregnancy…category B
- Watch for PCN allergies
- Adults: 250, 500 and 875 mg
  - ★ Dose of clavulanate varies
- Children <100 pounds: oral suspension 25-45 mg/kg divided into 2 doses
- Covers *Staph*, *Strep* and *Haemophilus influenzae*

Azithromycin (Zithromax)

- Macrolide antibiotic (erythromycin is prototype)
- Drug of choice in PCN sensitive patients
- All age groups and pregnancy category B
- No renal adjustment

- Adult:
  - 250 mg bid (day1), 250 mg qd (day 2-5), 6 pack
  - 500 mg qd x 3 days, tri-pack
- Children<16: 10 mg/kg (day1), 5 mg/kg (day 2-5)

- Covers *Staph*, *Strep* and *Haemophilus influenzae*
- Better tolerated than erythromycin, little GI upset
- Chlamydia…1 g qd

Zithromax (azithromycin)

- "The Vegas Drug"- Chlamydia…1 g qd

Cephalexin (Keflex)

- Cross reaction with PCN sensitive patients
  - Approximately 3 – 10%
- 1st generation, moderately affective against PCN-ase
- Good for Gram +, +/- for *Haemophilus* (-)
- Available in 250 and 500 mg

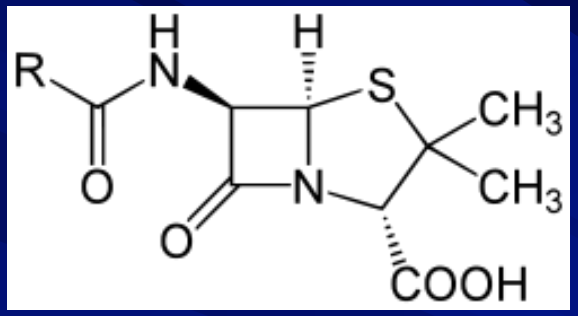
- Category B
- Adult: typically, 500 mg bid x 1 week
  - Maximum 4 g in 24 hrs
- FYI…Drug of choice for blow out fractures

Cefuroxime (Ceftin)

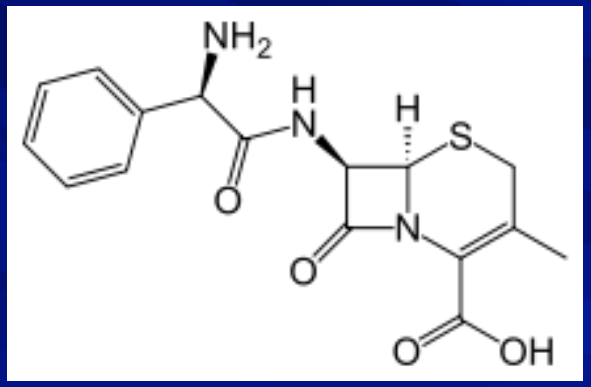
- 2nd generation
- Better for *Haemophilus (-)*

- Children: 3 months to 12 years old, oral suspension 15 mg/kg divided into 2 doses x 10 days
- Available in 125, 250 and 500 mg
  - ✶ FYI: adults typically 250 mg bid x 10 days
- Category B

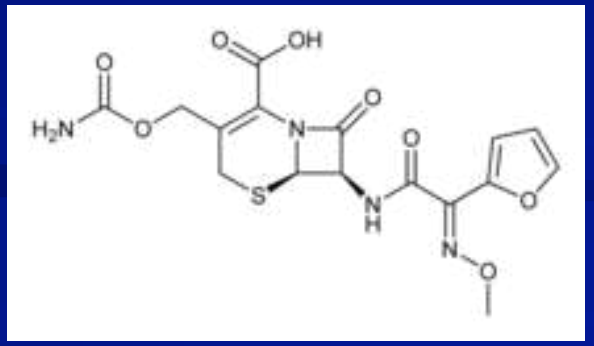
Cross Reaction



PCN



Keflex



Ceftin

Sulfa Drugs

- Limited use…last line of defense

- Bactrim SS
  - 400 mg sulfamethoxazole/ 80 mg trimethoprim
  - 1-2 tab PO bid
- Bactrim DS (double strength)
  - 800 mg sulfamethoxazole/ 160 mg trimethoprim
  - 1 tab PO bid

Ciprofloxacin (Cipro)
Levofloxacin (Levaquin)

- In my opinion, an end of the line, antibiotic to use…allergic to PCN, cephlosporins, macrolides…
- Really effective, because they are BROAD
- Would avoid if pregnant, BF, and in kids
  - Only use 18 years or older (oral)

- Cipro and Levaquin available in 250, 500 and 750 mg
  - Cipro 750 mg for only severe infections (usually life-threatening pneumonia)
- 500 mg bid x 1 week-Cipro
- 500 mg qd x 1 week-Levaquin
- Levaquin-tendon ruptures

Fluoroquinolone ADRs

- Retinal detachment (1 per 2,500 pts)
  - WHAT?!?
    - Mechanism is possible through destruction of collagen and connective tissue…
- QT prolongation in newer agents
- Photosensitivity
- Tendon rupture
  - Watch shoulders, wrists, Achilles

Dacryocystitis

Text me your answer 814-931-2030

Patient as a severe allergic reaction to Penicillin and Keflex (Epipen)

Which antibiotic would you use?

A. Augmentin
B. Azithromycin
C. Cephalexin
D. Bactrim
E. Cipro

- Remember…patient allergic to PCN and Keflex

- Treatment
  - ★ Polytrim QID OD
  - ★ Zithromax
    - Disp: 5 day z-pak
    - Use as directed PO

Text me your answer 814-931-2030

- Dilation and Irrigation
  - ★ Contraindication or indication?
- Confirmed nasolacrimal duct blockage
  - ★ DCR, dacryocystorhinostomy

What group of antibiotics are we missing?

Text me your answer 814-931-2030

When we use doxycycline or minocycline for dry eye disease, ocular surface, and/or meibomian gland dysfunction. What property of this pharmaceutical are we benefitting from?

A. Bacteriostatic action – anti-infective
B. Anti-protozoan action – Malaria
C. Works for Methicillin-resistant Staphylococcus aureus (MRSA)
D. Anti-inflammatory action – inhibiting bacterial lipases
E. I don't know

Treatment Failure

- If you continue to think of doxycycline and minocycline as antibiotics, treatment failure will be the result
- From this point on consider them a steroid

48-year-old man
OU red, gritty, sandy and dry feeling

Va	20	20
20		
cc		20

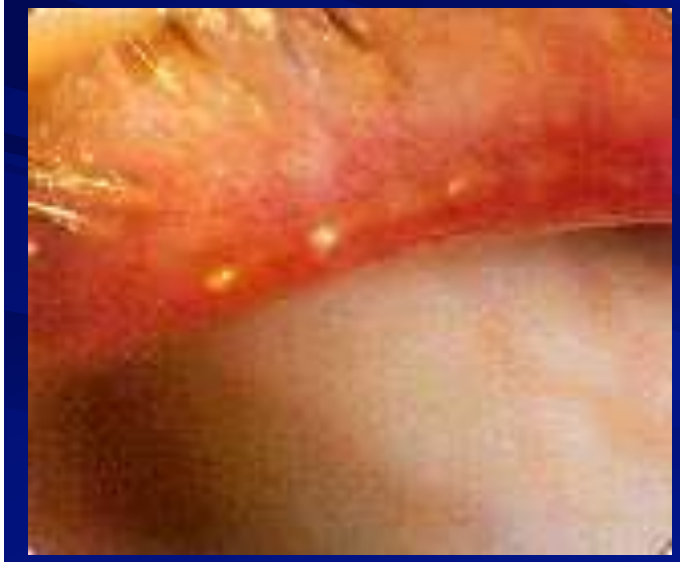
Current Correction
R -2.00 sphere
L -3.00 sphere

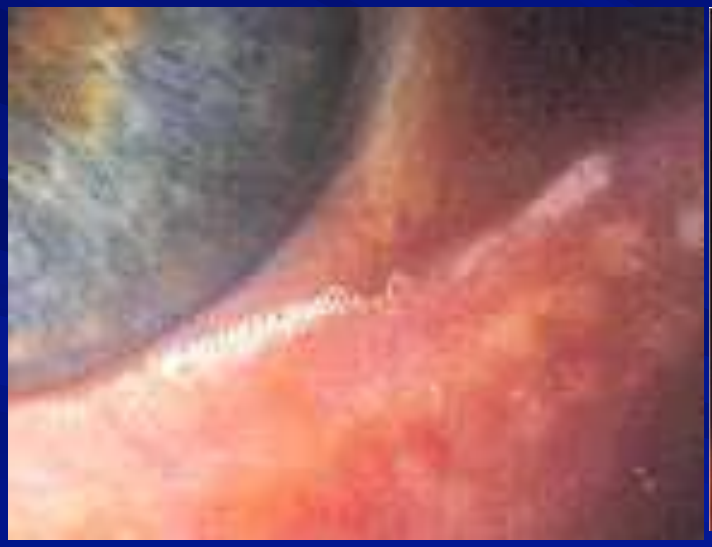
EOMS: full, unrestricted
CT: ortho D/N

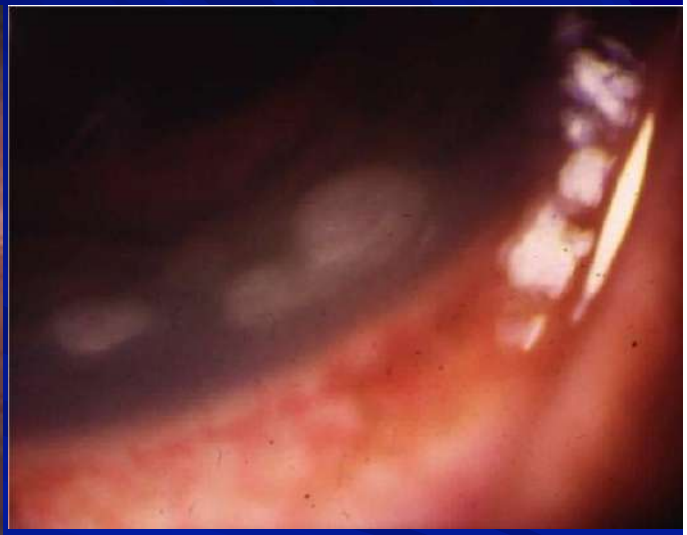
PERRL (-)APD
CF: full by FC OU

- Diagnosis
  - Rosacea
- What findings support your diagnosis?
  - Telangiectasias
  - Erythema of the cheeks, forehead and nose
  - Rhinophyma
    - Indicates chronic
- Let us get a closer look

A Closer Look







Rosacea Blepharitis
(Inflammatory Blepharitis, MGD)

- Diagnosis?
- Treatment?
  - In my opinion, most under treated condition
  - Warm compresses
  - Lid hygiene
  - Artificial tears
  - Omega 3 fatty acid
    - EPA and DHA total 1500 mg (1000 mg minimum)
  - Dermatological consult (Acne Rosacea)
  - Oral antibiotics…???
    - Which one and why??

Tetracycline Analog

Staph Aureus
Staph Epidermidis

Lipase

Meibomian Gland Secretions
(Lipid)

Turbid
Inspissated MG

Marginal Foam
(Soap)

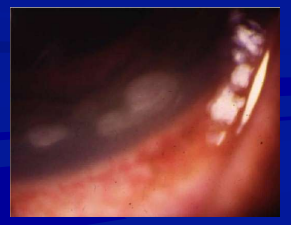
Phospholipids

Arachidonic Acid

Prostaglandins
Thromboxines

Leukotrienes

How About Steroids?



Minocycline / Doxycycline

- Drug of choice for marginal inflammatory blepharitis, posterior blepharitis, MGD, evaporative disease
- AB, anti-inflammatory and anti-collagenase

- No renal adjustment
- 50-100 mg qd-bid 2-12 weeks (pulse)
  - Lower maintenance dose
- 20 mg Periostat (Doxycycline)
  - Helpful in those with stomach or GI sensitivity
  - Excellent for those requiring long maintenance dose

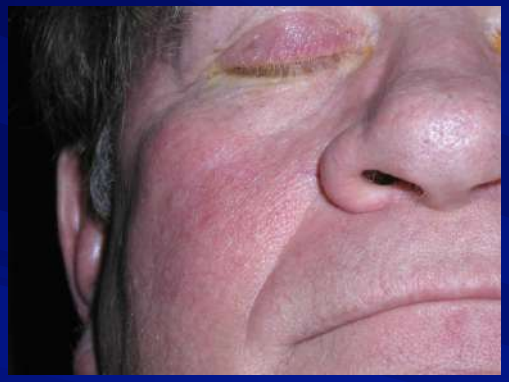
My Paradigm for Minocycline / Doxycycline

- Status of MG
  - ★ Inspissated
  - ★ Turbid
  - ★ Clear
- Minocycline / Doxycycline Paradigm
  - ★ Maximum dosage for 2-12 weeks (pulse)
    - 100 mg BID, QD
  - ★ 50-100mg qd while turbid
  - ★ 20 mg longer treatments
    - Periostat (Doxycycline)
  - ★ 20 mg if maintenance dose needed

Customize Treatment

- 50 mg Minocycline with pill cutter (25 mg)
- Oracea- 40 mg of Doxycycline total
  - 30 mg immediate release
  - 10 mg sustained release
- AzaSite (azithromycin opthalmic solution) 1.0%
  - Initiate early in treatment
  - Adjunctive when patient is already on Doxycycline
  - Alternative in states that do not have oral therapeutic licensure

Successfully Treated



- Warm Compresses
- Lid Scrubs
- Artificial Tears, Systane Balance
- Omega 3 (1500 EPA and DHA)
- Mino 100 mg PO 6 weeks, 50 mg 3 months, 20 mg maintenance (Doxy)
- Steroids, Tobradex qid (5 weeks with taper)
  - Moderately red and thickened lid margins
  - Marginal infiltrates

Hyclate vs Monohydrate

- I get calls from the pharmacist
  - Doxycycline
    - Doryx
      - Enteric coated hyclate pellet
    - Adoxa
      - Monohydrate

Doxycycline and Minocycline
Adverse Drug Reactions

- Enhanced photosensitivity
- Avoid in children and pregnancy (Category D)
- Can interfere with how penicillin kills bacteria
- Enhances the effects of
  - Coumadin
  - Digoxin
- ~~Idiopathic~~ Secondary intracranial hypertension
  - Pseudotumor cerebri
  - Isotretinoin (Accutane) – for severe acne and doxy/mino increase this risk
- Hyperpigmentation

- Antacids that contain aluminum, calcium, magnesium, bismuth subsalicylate, and iron may inhibit doxy/mino
  - Same for seizure meds like barbiturates, carbamazepine, phenytoin

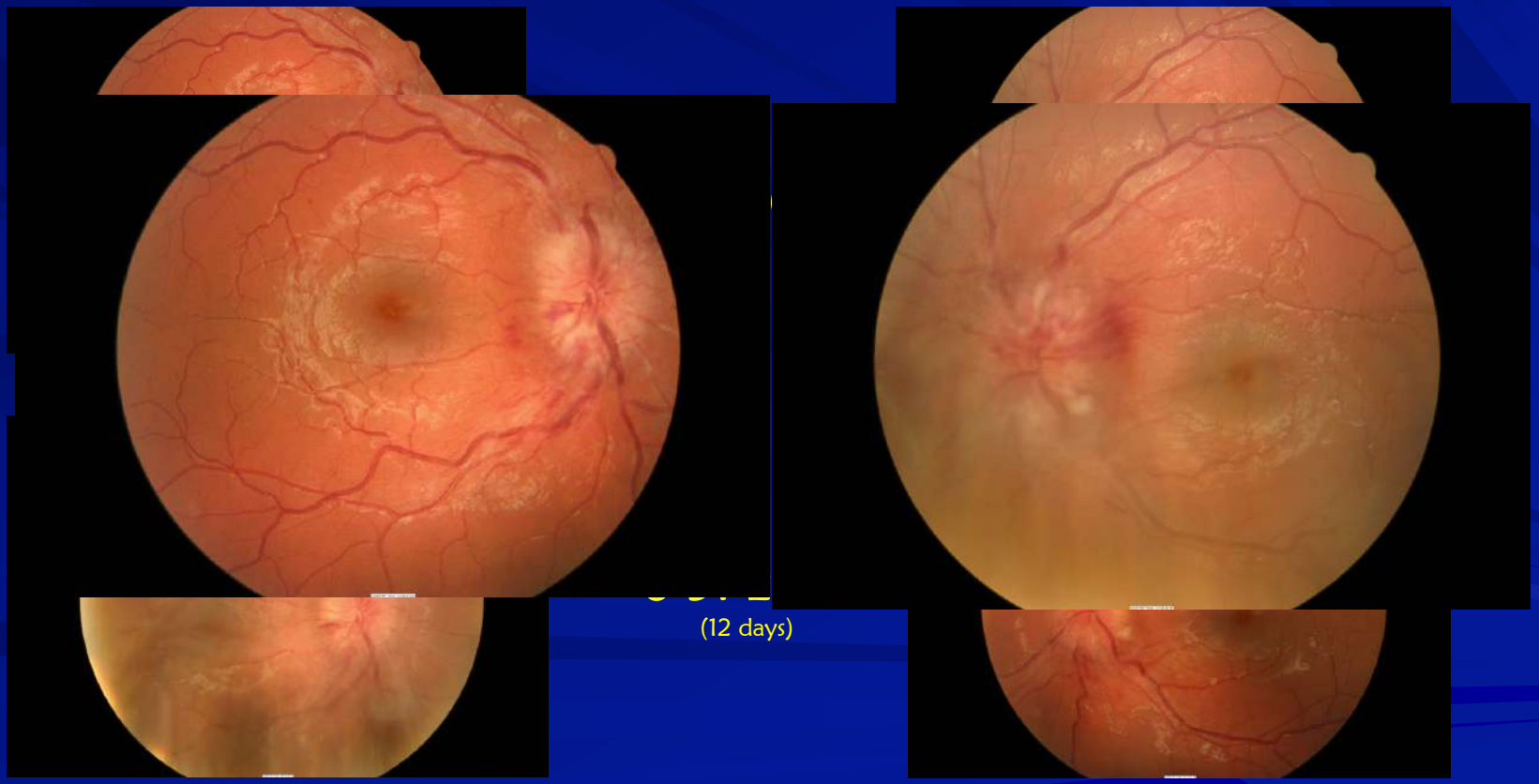
Text me your answer 814-931-2030

I have seen a patient with optic nerve head edema from doxycycline or minocycline:

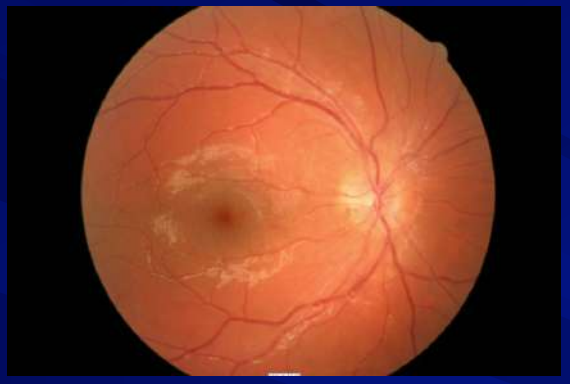
A. Yes
B. No
C. I don't know

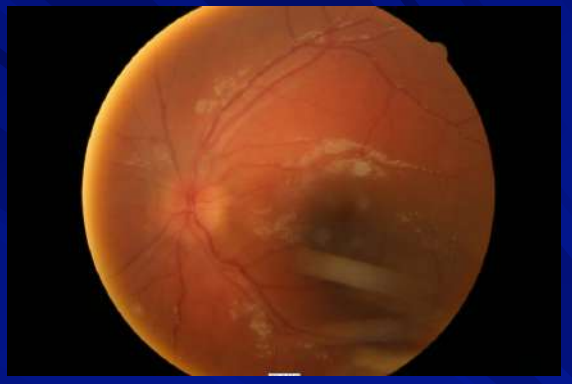
Benign intracranial hypertension

"It's not rare if it's in your chair"

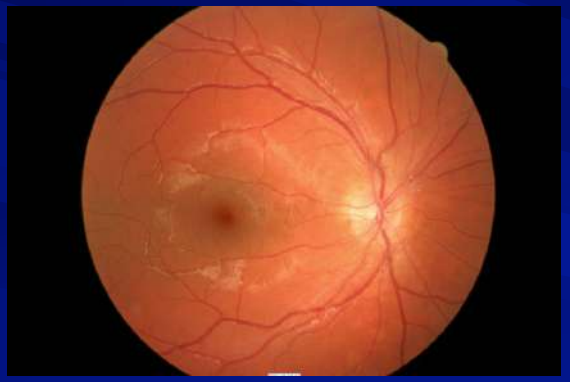


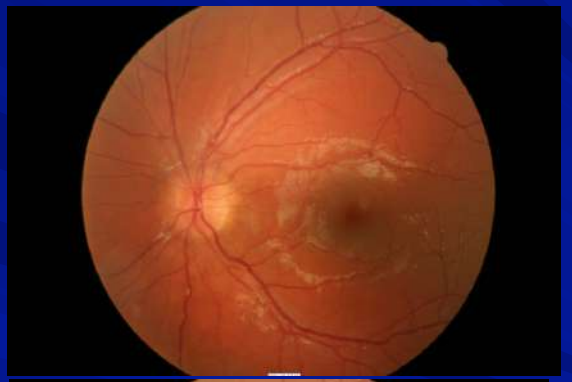
(12 days)



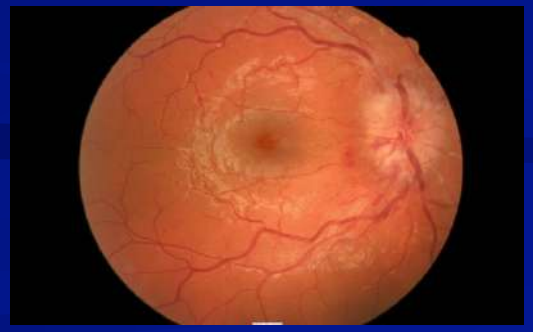


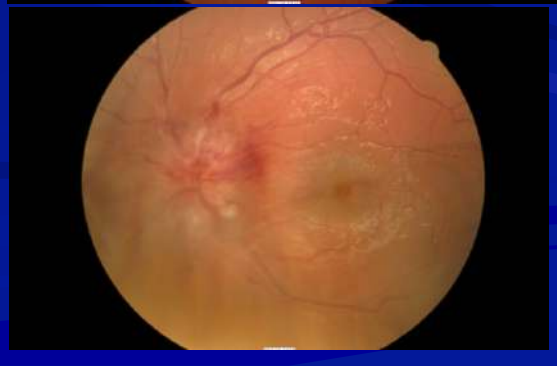
9-13-2010
25 days





10-6-2010
48 days

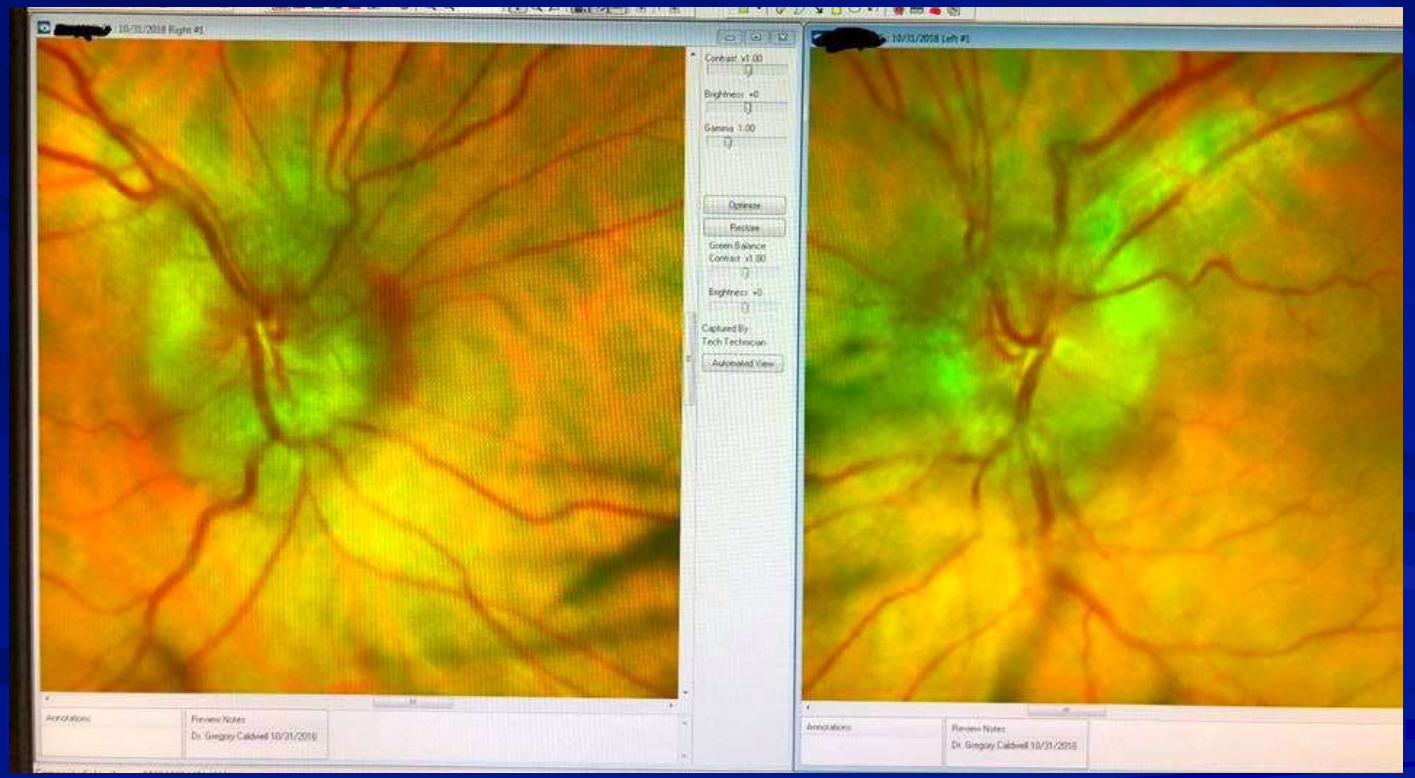




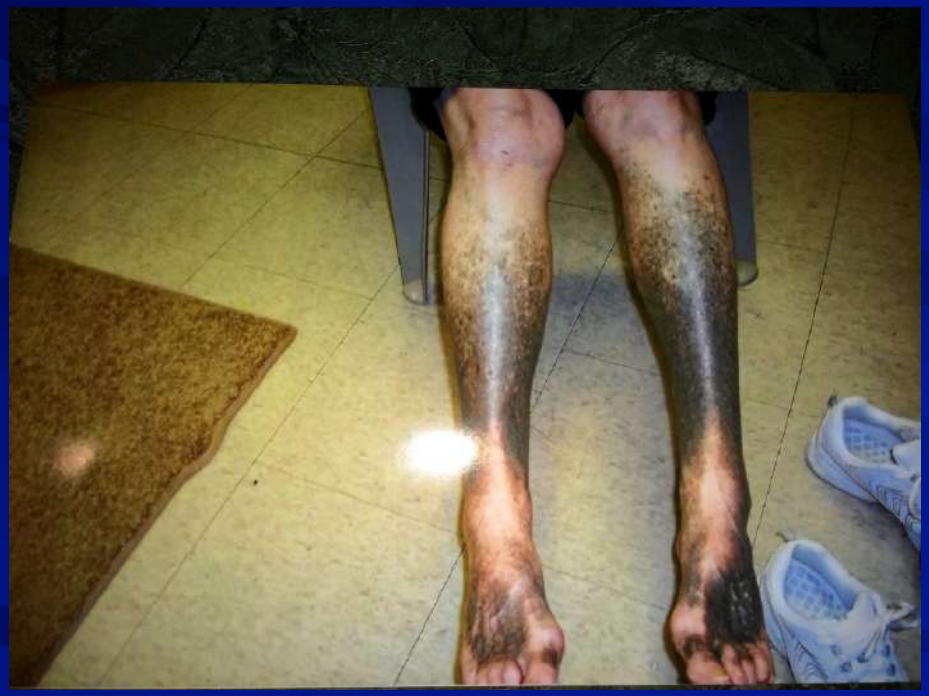
8-19-2010

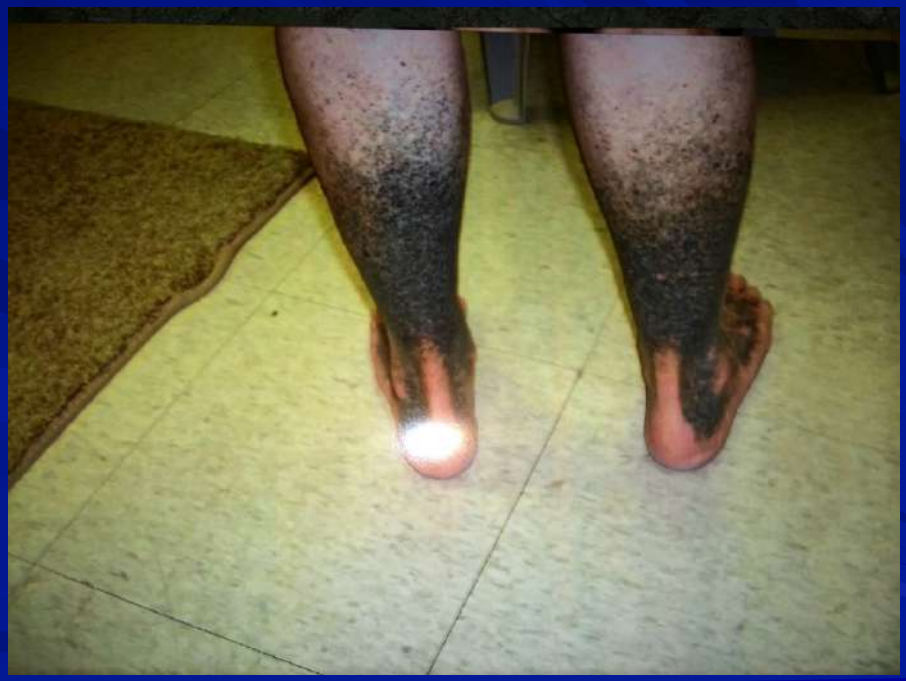
Minocycline Optic Nerve Edema

Minocycline Optic Nerve Edema

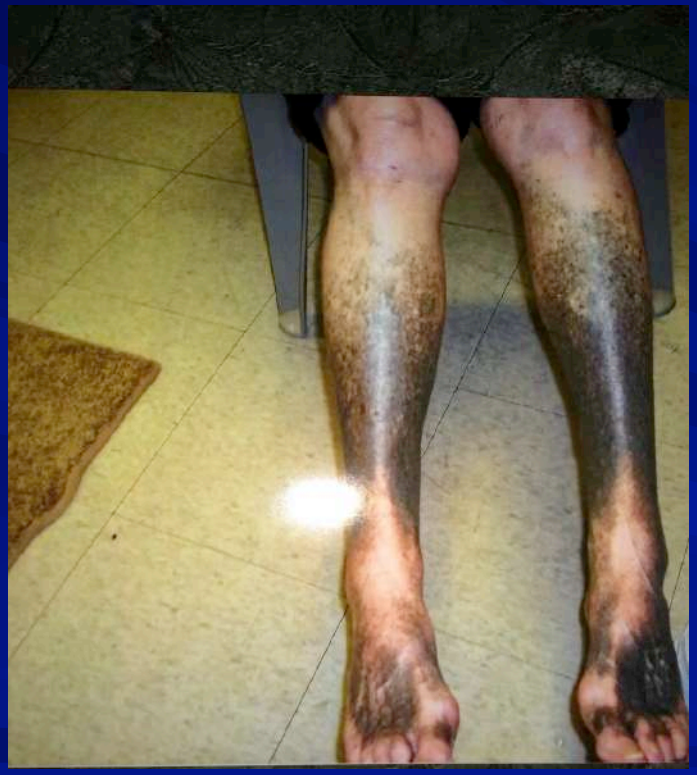


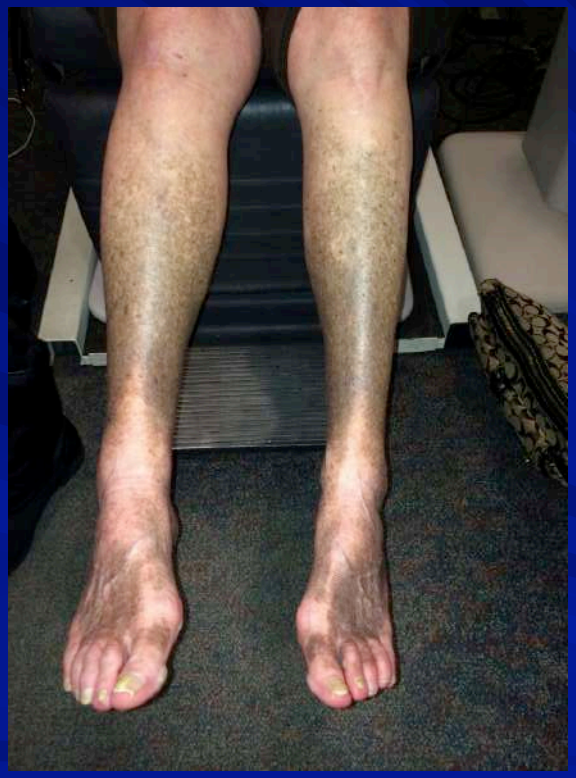
OMG



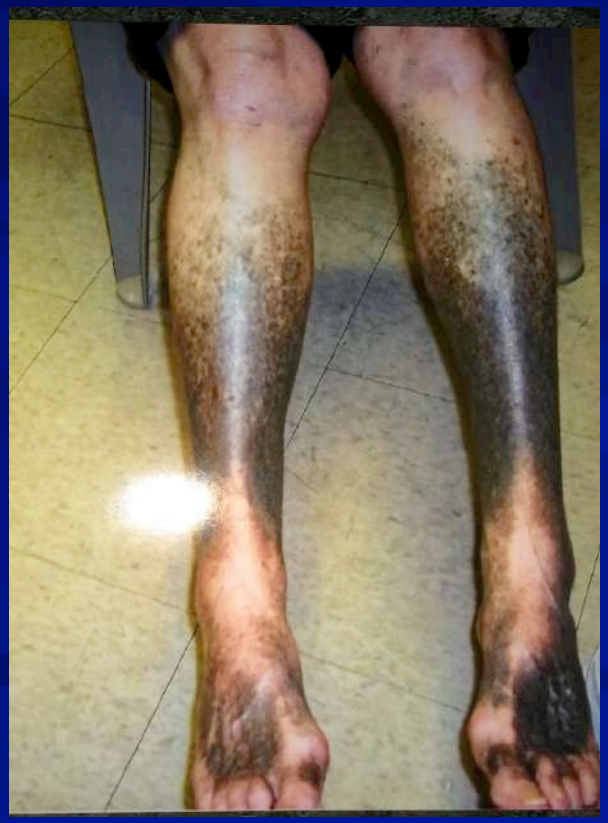


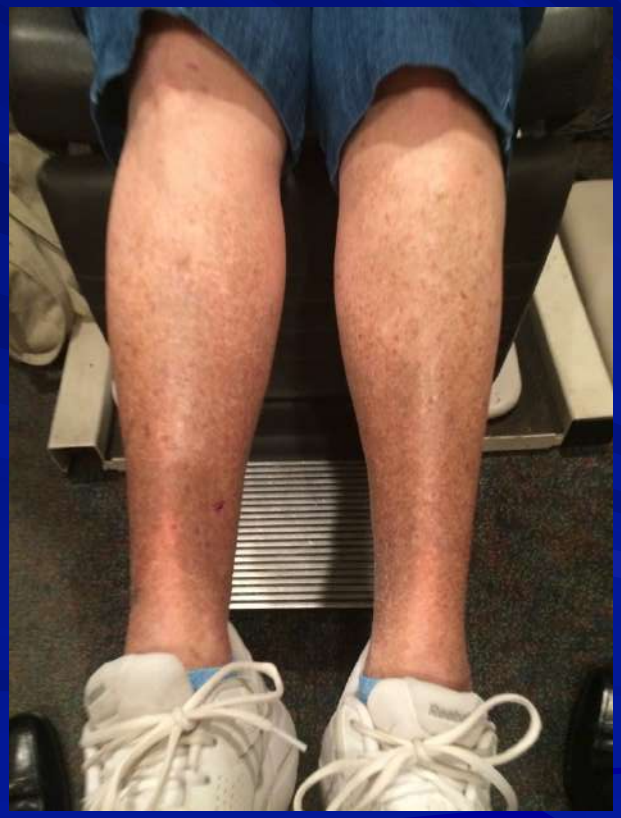
6 Months Later





1 Year Later





Delafloxacin™ (Baxdela)

- A fluoroquinolone antibiotic for acute bacterial skin and skin structure infections
  - Approved 2017 – Melinta Therapeutics
  - Available orally and intravenously
  - Adverse effects: SO NEW…but in clinical trials, the only ophthalmic side effects that were noted = blurred vision!
    - Only time will tell if retinal detachment is something to worry about with this new FQ!

Nuzyra™ (omadacycline)

- Approved 2018
- Tetracycline antibiotic
- Approved for PO/IV treatment of patients with bacterial skin infections or community-acquired bacterial pneumonia

- Chelation issues JUST like other tetracyclines!
- ADRs: Nausea, vomiting, diarrhea, constipation, insomnia

Seysara™ (sarecycline)

- Approved 2018
- Tetracycline drug
- Indicated for the treatment of inflammatory acne in non-nodular, moderate to severe acne vulgaris

- Can be taken WITH or WITHOUT food!

- ADRs: nausea

Xerava™ (eravacycyline)

- Approved 2018
- Tetracycline antibiotic
- Indicated for the treatment of intra-abdominal infections in adults

- IV ONLY

Orals in Herpetic Eye Disease

- Valtrex
- Acyclovir
- Famvir

- Neurontin
- Lyrica
- Doxycycline
- L-Lysine
- Tagamet
- Tricyclic antidepressants
  - Amitriptyline, nortriptyline

Fun Facts About Herpes

- Are a leading cause of human viral disease
  - Second only to influenza and cold viruses
- There are more than 130 herpes viruses identified
  - 8 infect humans (9 if you count HHV-6A and HHV-6B as two separate)
  - 5 infect the eye
    - Herpes simplex 1
    - Herpes simplex 2
    - Varicella zoster
    - Epstein Barr
    - Cytomegalovirus
- USA 25% of the population is seropositive for HSV by 4 years old
  - Nearly 100% are seropositive by age 60
  - Lifetime prevalence of ocular manifestation in all HSV infected people is 1%

8 Humans- 5 Eye

Viruses of Humans	Common Name	Subfamily
Human herpesvirus 1	Herpes simplex type1	alpha
Human herpesvirus 2	Herpes simplex type 2	alpha
Human herpesvirus 3	Varicella-zoster	alpha
Human herpesvirus 4	Epstein-Barr	gamma
Human herpesvirus 5	Cytomegalovirus	beta
Human herpesvirus 6/7	exanthum subitum roseola infantum	beta
Human herpesvirus 8	Kaposi's Sarcoma-assoc.	gamma

Viruses of Humans	Common Name	Subfamily
Human herpesvirus 1	Herpes simplex type1	alpha
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Human herpesvirus 4	Epstein-Barr	gamma
Human herpesvirus 5	Cytomegalovirus	beta
Human herpesvirus 6/7	exanthum subitum roseola infantum	beta
Human herpesvirus 8	Kaposi's Sarcoma-assoc.	gamma

Herpes Viruses are Classified by Their Location in the Latent State

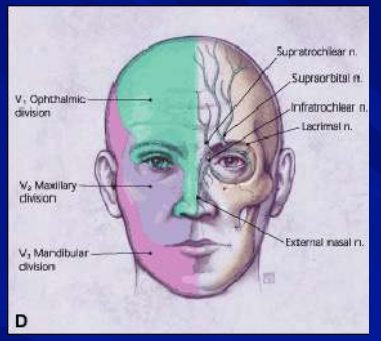
Human herpes type	Name	Sub Family	Target cell type	Latency	Transmission
1	Herpes simplex-1 (HSV-1)	Alphaherpesvirinae	Mucoepithelia	Neuron	Close contact
2	Herpes simplex-2 (HSV-2)	Alphaherpesvirinae	Mucoepithelia	Neuron	Close contact usually sexual
3	Varicella Zoster virus (VSV)	Alphaherpesvirinae	Mucoepithelia	Neuron	Contact or respiratory route
4	Epstein-Barr Virus (EBV)	Gammaherpesvirinae	B lymphocyte, epithelia	B lymphocytes	Saliva
5	Cytomegalovirus (CMV)	Betaherpesvirinae	Epithelia, monocytes, lymphocytes	Monocytes, lymphocytes and possibly others	Contact, blood transfusions, transplantation, congenital
6	Herpes lymphotropic virus	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Contact, respiratory route
7	Human herpes virus-7 (HHV-7)	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Unknown
8	Human herpes virus-8 (HHV-8) Kaposi's sarcoma-associated herpes virus (KSHV)	Gammaherpesvirinae	Endothelial cells	Unknown	Exchange of body fluids?

Herpes Simplex Virus Keratitis

- Is a leading cause of corneal blindness in the United States
  - Primarily caused by HSV-1 (65%)
- Keratitis nomenclature
  - Infectious epithelial keratitis
    - It's not critical to determine HSV 1 or 2
  - Stromal keratitis
  - Endotheliitis
  - Neurotrophic keratopathy

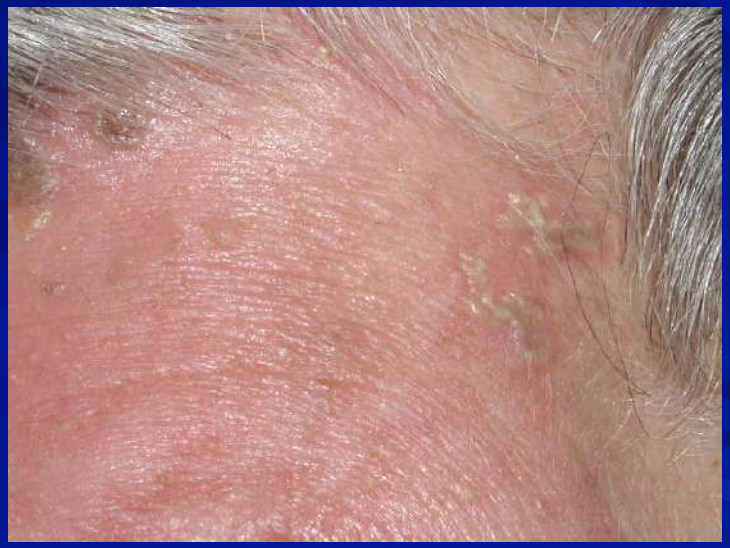
Varicella-Zoster Virus (VZV)

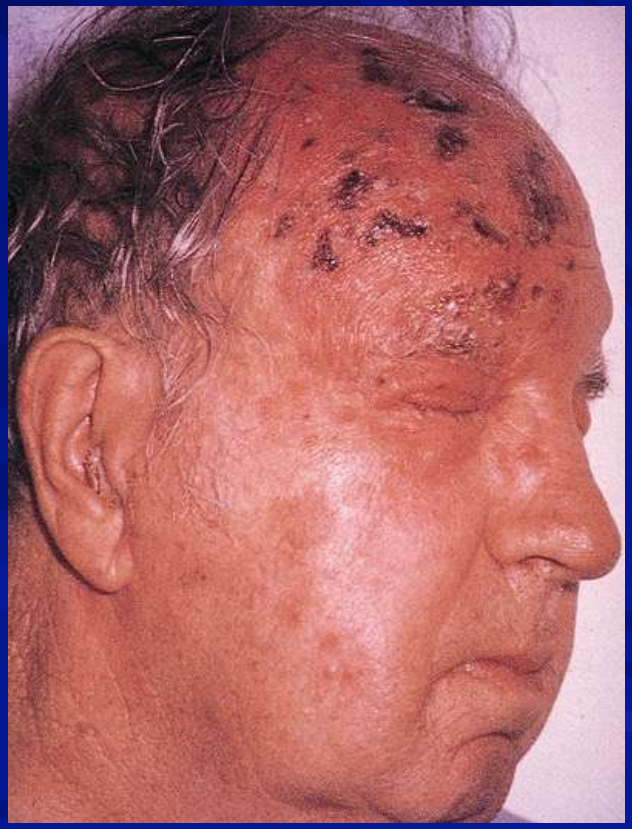
- AKA: Herpes Zoster Virus or Herpes Human Virus 3
- Vesicles on tip of nose indicate nasociliary involvement
  - High risk of ocular manifestations



Varicella-Zoster Virus (VZV)

- The best time to diagnose and treat



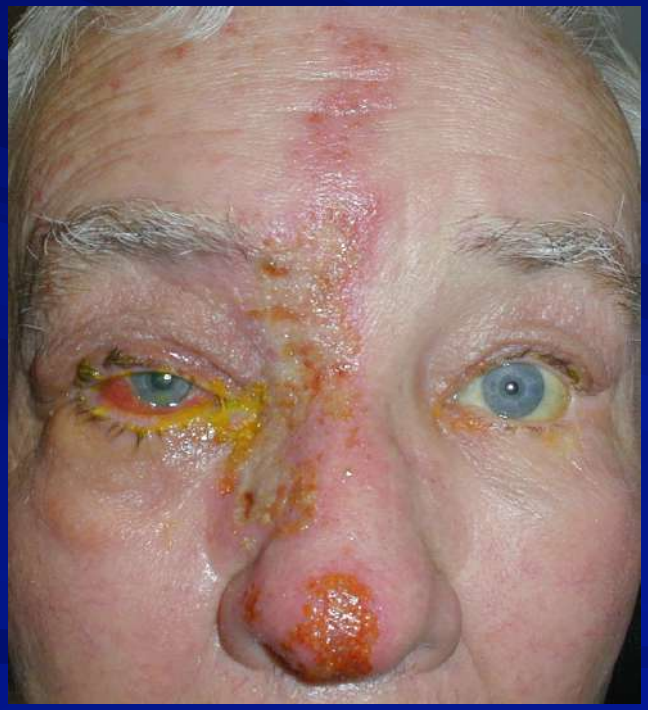


Text me your answer 814-931-2030

Ever wonder why a Primary Care Physician sends you with Herpes Zoster already on oral Valtrex and prednisone?

A. Yes
B. No
C. Never happened to me

Varicella-Zoster Virus (VZV)



- Vesicles on tip of nose indicate nasocilliary nerve involvement
  - High risk of ocular manifestations
- Ocular findings associated with VZV
  - Episcleritis
  - Scleritis
  - Keratitis
  - Uveitis
  - Iris atrophy
  - Glaucoma
  - Vitritis
  - Retinitis
  - Choroiditis
  - Optic neuritis
  - CN palsy

Renal Impairment

- Identify patients on hemodialysis
- Adjustment made by patient's creatinine clearance (CrCl)…ml/min
  - Work with patient's PCP/Internist

Zovirax (acyclovir)

- Good for simplex and zoster
- Available in 200, 400 and 800 mg, IV
- Dosage: 800 mg/5 times/day (4 grams daily)
  - Poor GI absorption
- Maintenance dose: 200-400 mg bid
- Caution if impaired renal function
  - ★ Excreted by kidneys
- Category B

Off-Label

- Valtrex and Famvir used for the eye
  - Off label
  - Only approved for genital herpes
  - Won't find dosage in PDR for ocular usage

Famvir (famciclovir)

- Available in 125, 250 and 500 mg
- Dosage: Zoster 500 mg tid
  Recurrent Simplex 125-250 mg bid
- Caution if impaired renal function
- Category B

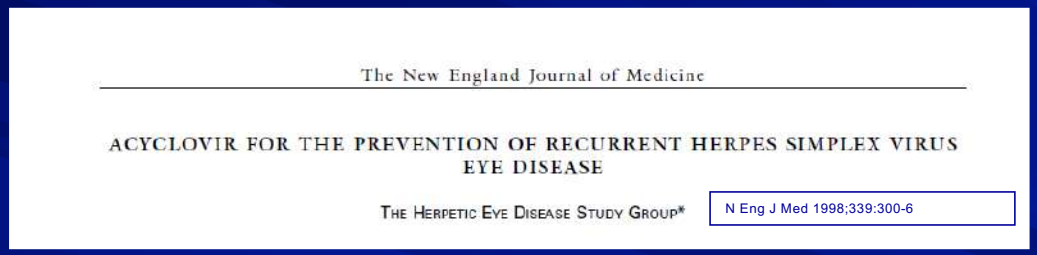
- No longer available via Norvartis in USA as brand name

Valtrex (valacyclovir)

- Pro-drug of acyclovir
- Available in 500 and 1000 mg
- GI upset
- HSV-1, HSV-2, VZV
- Dosage: 1g tid x 1 week (3 grams daily)
- Caution if impaired renal function
- Category B

Beside the dosing frequencies…

- What is different about the oral antivirals?



The New England Journal of Medicine

ACYCLOVIR FOR THE PREVENTION OF RECURRENT HERPES SIMPLEX VIRUS EYE DISEASE

THE HERPETIC EYE DISEASE STUDY GROUP*

N Eng J Med 1998;339:300-6

- Main reason for early discontinuation of oral acyclovir in HEDS
  - Gastrointestinal side effects
  - Rash

Many patients on oral acyclovir have GI symptoms

Text me your answer 814-931-2030

Which oral anti-viral is lactose free?

A. Acyclovir
B. Famvir
C. Valtrex
D. They all have lactose

Acyclovir vs. Valacyclovir vs. Famciclovir

What is the difference?

ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analogue active against herpesviruses. ZOVIRAX Capsules, Tablets, and Suspension are formulations for oral administration. Each capsule of ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.

Acyclovir

Zovirax® contains lactose

Presence or absence of lactose in generic acyclovir varies

VALTREX (valacyclovir hydrochloride) is the hydrochloride salt of the *L*-valyl ester of the antiviral drug acyclovir.

VALTREX Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

Valacyclovir

Valtrex® and all generics are free of lactose

FAMVIR tablets contain 125 mg, 250 mg, or 500 mg of famciclovir, together with the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.

Generics available in the US contain lactose

* In Europe you can get generic famciclovir without lactose (Teva Pharmaceuticals, Israel)

Acyclovir vs. Valacyclovir vs. Famciclovir

What is the difference?

CNS Effects in Elderly Patients

- Acyclovir and valacyclovir carry a higher risk of CNS adverse effects in the elderly:
  - Agitation
  - Hallucinations
  - Confusion
- Clinical Take Home Point:
- Consider famciclovir in older patients who CNS side effects with acyclovir or valacyclovir
- Other major concern with elderly patients is age-related reduced kidney function

24-48 hours

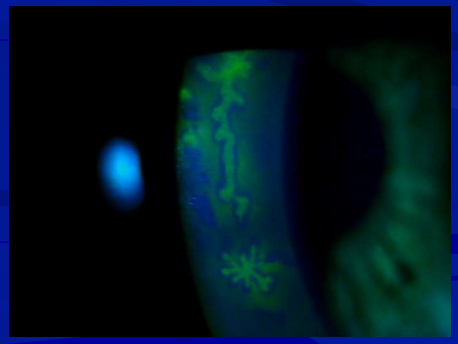
- Zirgan
- Viroptic

- Orals only
- Orals and Amniotic Membrane

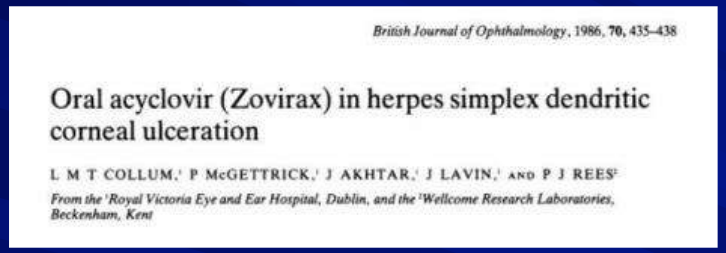
Is there a difference in efficacy between topical and orals in the various forms of ocular herpes?

Ganciclovir ophthalmic gel

Oral antivirals:
Acyclovir
Valacyclovir
Famciclovir



Epithelial keratitis
There seems to be equivalence



British Journal of Ophthalmology, 1986, **70**, 435–438

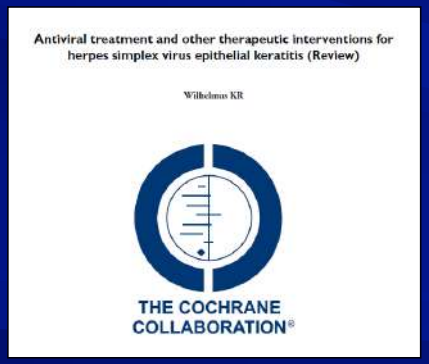
Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration

L M T COLLUM,[1] P McGETTRICK,[1] J AKHTAR,[1] J LAVIN,[1] AND P J REES[2]

From the [1]Royal Victoria Eye and Ear Hospital, Dublin, and the [2]Wellcome Research Laboratories, Beckenham, Kent

60 patients with HSV dendritic ulceration included a small number with stromal involvement keratitis randomized to oral vs. topical acyclovir

No statistically significant difference in to time to resolution (mean = 5 days)



Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis (Review)

Wilhelmus KR

THE COCHRANE COLLABORATION®

"Oral acyclovir alone appeared as effective as topical antiviral therapy in the treatment of simplex epithelial keratitis."

Oral delivery appears to get to corneal target even though it is an avascular tissue!

Cochrane Database Syst Rev 2010:8(12):1-198.

Vaccines

- Zostavax™ – live vaccine; 60 years and older
  - "the only game in town…"
    - 50-ish% effective; 1 dose
    - Efficacy wanes after 4-5 years
- Shingrix™ – has replaced Zostavax™
  - We are moving in the right direction!
  - Recommended for 50 years and older
    - 90+% effective?; 2 doses; IM; recombinant vaccine
    - Efficacy *seems* solid up to 7-8 years

Optometric Education Consultants

Oral Pharmaceuticals in Eye Care

"Pearls from an Optometrist and Pharmacist "

Greg Caldwell, OD, FAAO
Tracy Offerdahl, PharmD, Bpharm, RPh, FAAO

CE Sarasota 2023
Optometric Education Consultants
Saturday, March 4, 2023