


**Oral Antibiotics and Antivirals
in Eye Care**

"Discussion Between an Optometrist and Pharmacist"

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Mackinac Island
Optometric Education Consultants
Saturday, August 27, 2022



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Disclosures- Greg Caldwell, OD, FAAO
All relevant relationships have been mitigated

- The content of this activity was prepared independently by me - Dr. Caldwell
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Maculogix, Optovue, RVL, Heru
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- Dr. Offerdahl has the following financial disclosure:
 - Boiron: honorarium, webinar/speaker
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**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

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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 out weigh risks...avoid
- Category X- fetal abnormalities, risk>benefits...avoid

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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 embryofetal 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

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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

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Pre-June 30, 2015

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Post-June 30, 2015

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Post-June 30, 2015

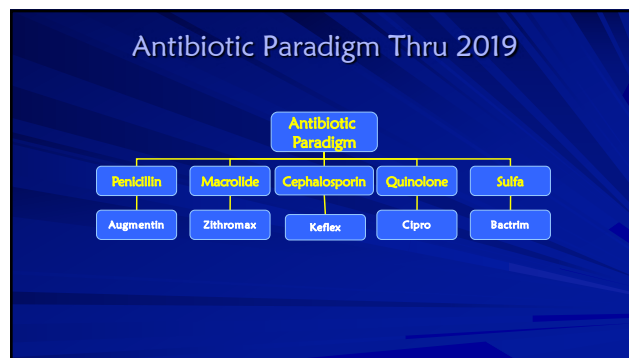
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Dacryocystitis

Rolling Question 1
Patient as a severe allergic reaction to Penicillin and Keflex (Epipen)
Which antibiotic would you use?

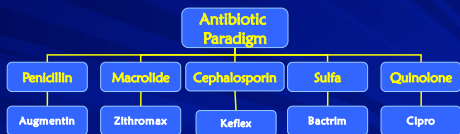
- A. Augmentin
- B. Azithromycin
- C. Cephalexin
- D. Bactrim
- E. Cipro

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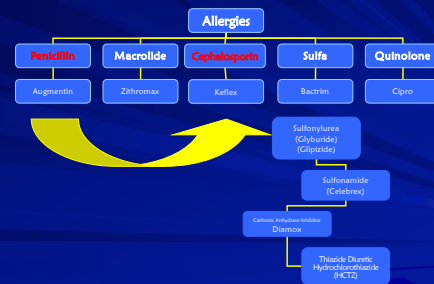
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Antibiotic Paradigm Changed 2020



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Cross Reaction



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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*

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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

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Zithromax (azithromycin)

- ~ "The Vegas Drug"- Chlamydia...1 g qd



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Cephalexin (Keflex)

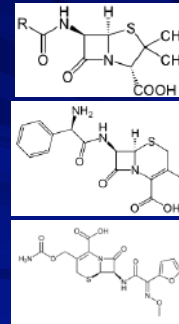
- ~ Cross reaction with PCN sensitive patients
 - * Approximately 3 - 10%
- ~ 1st generation, moderately effective against PCN-ase
- ~ Good for Gram +, +/- for *Haemophilus* (-)
- ~ Available in 250 and 500 mg
- ~ Category B
- ~ Adult: typically, 500 mg bid x 1 week
 - * Maximum 4 g in 24 hrs
- ~ FYI...Drug of choice for blow out fractures

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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

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Cross Reaction

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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

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Sulfa ADRs

- ~ Contraindicated in pregnancy and sickle cell disease
 - * Category C
- ~ High incidence of Steven-Johnsons Syndrome (SJS) and Toxic epidermal necrolysis (TEN)
- ~ Cross reaction with: oral hypoglycemics, CAI's, celebrex and thiazide diuretics...all sulfa based
 - * Reality?

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Ciprofloxacin (Cipro) Levofloxacin (Levaquin)

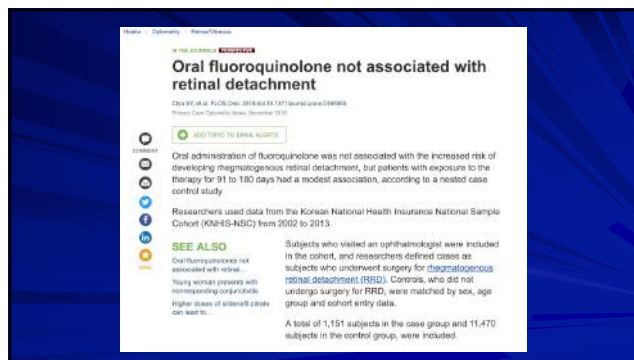
- ~ In my opinion, an end of the line, antibiotic to use...allergic to PCN, cephalosporins, macrolides...
- ~ Really effective, because they are BROAD
- ~ Would avoid if pregnant, BF, and in kids
 - * Only use 18 years or older (oral)
- ~ Cipro and Levaquin available in 250, 500 and 750 mg
 - * Cipro 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

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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

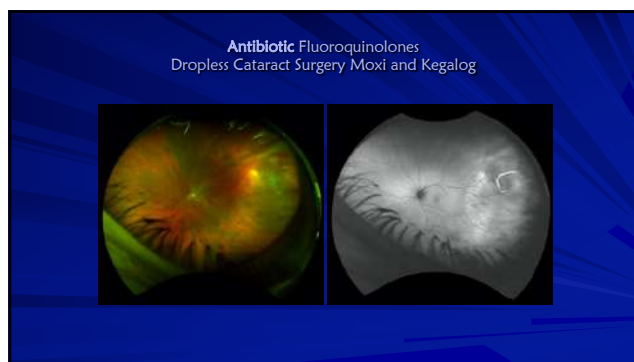
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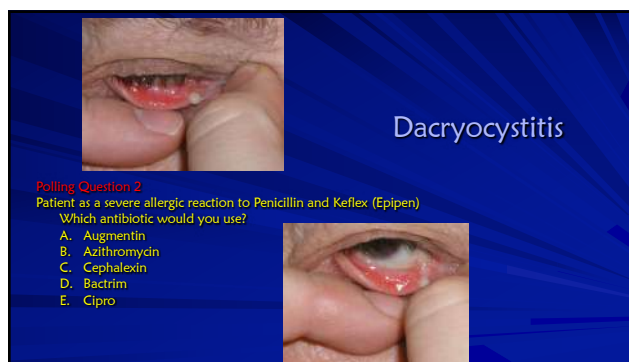
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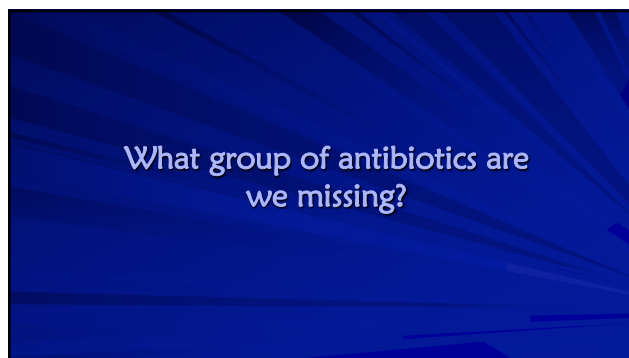
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Polling Question 4

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

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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

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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 PERRL (-)APD
CT: ortho D/N CF: full by FC OU

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

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A Closer Look

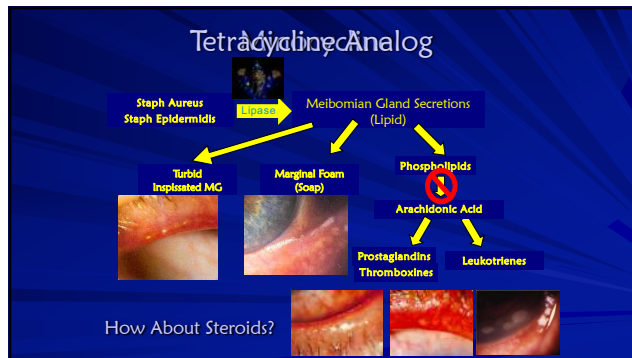


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Rosacea Blepharitis (Inflammatory Blepharitis, MGD)

- ~ 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??

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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

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My Paradigm for Minocycline / Doxycycline

<p>~ Status of MG</p> <ul style="list-style-type: none"> * Inspissated * Turbid * Clear 	<p>~ Minocycline / Doxycycline Paradigm</p> <ul style="list-style-type: none"> * Maximum dosage for 2-12 weeks (pulse) <ul style="list-style-type: none"> □ 100 mg BID, QD * 50-100mg qd while turbid * 20 mg longer treatments <ul style="list-style-type: none"> □ Periostat (Doxycycline) * 20 mg if maintenance dose needed
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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 ophthalmic solution) 1.0%
 - * Initiate early in treatment
 - * Adjunctive when patient is already on Doxycycline
 - * Alternative in states that do not have oral therapeutic licensure

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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 (Doxycycline)
- ~ Steroids, Tobradex qid (5 weeks with taper)
 - * Moderately red and thickened lid margins
 - * Marginal infiltrates

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Hyclate vs Monohydrate

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

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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
- **Hypertension**, 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



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Polling 5

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

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

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Benign intracranial hypertension "It's not rare if it's in your chair"

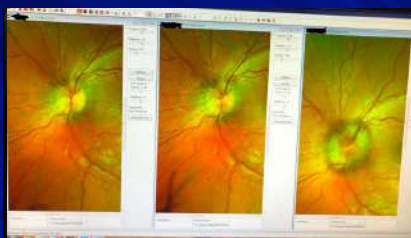


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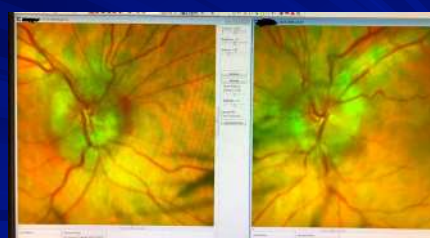
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Minocycline Optic Nerve Edema



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Minocycline Optic Nerve Edema



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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!

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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

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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

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Xerava™ (eravacycline)

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

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Orals in Herpetic Eye Disease

- ✓ Valtrex
- ✓ Acyclovir
- ✓ Famvir
- ✓ Neurontin
- ✓ Lyrica
- ✓ Doxycycline
- ✓ L-Lysine
- ✓ Tagamet
- ✓ Tricyclic antidepressants
 - Amitriptyline, nortriptyline

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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%

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8 Humans- 5 Eye

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

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Herpes Viruses are Classified by Their Location in the Latent State

Herpes Virus Type	Name	Sub Family	Typical Latent Site	Latency	Transmission
1	Herpes simplex 1 (HSV-1)	Alphaherpesvirinae	Nervous	Nervous	Close contact
2	Herpes simplex 2 (HSV-2)	Alphaherpesvirinae	Nervous	Nervous	Close contact (sexually transmitted)
3	Varicella-Zoster virus (VZV)	Alphaherpesvirinae	Nervous	Nervous	Contact with respiratory tract
4	Epstein-Barr virus (EBV)	Gammaproteovirinae	B lymphocytes, epithelial	B lymphocytes	Saliva
5	Cytomegalovirus (CMV)	Betaherpesvirinae	Epithelial, mononuclear, lymphocytes, and possibly others	Mononuclear lymphocytes and possibly others	Contact, blood, transfusion, congenital
6	Herpes lymphotropic virus	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Contact, respiratory route
7	Human herpes virus 8 (HHV-8)	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Unknown
8	Kaposi's sarcoma-associated herpes virus (KSHV)	Gammaproteovirinae	Endothelial cells	Unknown	Contact with body fluids

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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

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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



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Varicella-Zoster Virus (VZV)

- ~ The best time to diagnose and treat



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Polling 6

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

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Varicella-Zoster Virus (VZV)



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

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Renal Impairment

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

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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

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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

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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

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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

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Beside the dosing frequencies...

- ~ What is different about the oral antivirals?



- ~ Main reason for early discontinuation of oral acyclovir in HEDS
 - ~ Gastrointestinal side effects
 - ~ Rash
- ~ Many patients on oral acyclovir have GI symptoms

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Polling Question 7

- Which oral anti-viral is lactose free?
- A. Acyclovir
 - B. Famvir
 - C. Valtrex
 - D. They all have lactose

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Acyclovir vs. Valacyclovir vs. Famciclovir
What is the difference?

Acyclovir is the first oral antiviral, a synthetic nucleoside analogue active against herpesviruses. ZOVIRAS (Acyclovir, Teva) and its generic are the standard for the treatment of herpes simplex virus (HSV) infections. ZOVIRAS contains 200 mg of acyclovir and the inactive ingredients contain lactose, mannitol, croscarmellose, and other inert fillers. The capsule shell contains gelatin, titanium dioxide, and iron oxides. ZOVIRAS is not a controlled substance.

Valacyclovir is a prodrug of acyclovir, a synthetic nucleoside analogue active against herpesviruses. VALTREX (Valacyclovir, Teva) and its generic are the standard for the treatment of herpes simplex virus (HSV) infections. VALTREX contains 500 mg of valacyclovir and the inactive ingredients contain lactose, mannitol, croscarmellose, and other inert fillers. The capsule shell contains gelatin, titanium dioxide, and iron oxides. VALTREX is not a controlled substance.

Famciclovir is a prodrug of acyclovir, a synthetic nucleoside analogue active against herpesviruses. FAMCICLOVIR (Famciclovir, Teva) and its generic are the standard for the treatment of herpes simplex virus (HSV) infections. FAMCICLOVIR contains 250 mg of famciclovir and the inactive ingredients contain lactose, mannitol, croscarmellose, and other inert fillers. The capsule shell contains gelatin, titanium dioxide, and iron oxides. FAMCICLOVIR is not a controlled substance.

Generics available in the US contain lactose
* In Europe you can get generic famciclovir without lactose (Teva Pharmaceuticals, Israel)

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Acyclovir vs. Valacyclovir vs. Famciclovir
What is the difference?

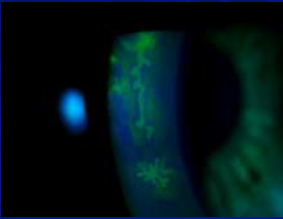
CNS Effects in Elderly Patients

- 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

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24-48 hours


- Zirgan
- Viroptic
- Orals only
- Orals and Amniotic Membrane



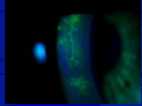
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Is there a difference in efficacy between topical and orals in the various forms of ocular herpes?

Ganciclovir ophthalmic gel



Oral antivirals:
Acyclovir
Valacyclovir
Famciclovir



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Epithelial keratitis
There seems to be equivalence


Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration

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 time to resolution (mean = 5 days)

"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!



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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

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 <p>Optometric Education Consultants</p>	<p>Questions? Thank You!</p> <p>Oral Antibiotics and Antivirals in Eye Care</p> <p>"Discussion Between an Optometrist and Pharmacist"</p> <p>Greg Caldwell, OD, FAAO Tracy Offerdahl, PharmD, Bpharm, RPh, FAAO</p> <p>Mackinac Island Optometric Education Consultants Saturday, August 27, 2022</p> 
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