


**Herpes A to Z
for the Eye Care Provider**


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Primary Eye Care Conference
(Pittsburgh)
Optometric Education Consultants
Saturday, February 17, 2024



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

- Lectured for: Alcon, B&L, BioTissue, Dompé
- Disclosure: Receive speaker honorariums
- Advisory Board: Dompé, ImmunoGen, Iveric
- Disclosure: Receive participant honorariums
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
- Disclosure: Non-salaried financial affiliation with Pharnanex
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
- The content of this activity was prepared independently by me - Dr. Caldwell
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My Practice

I am a clinician first then a scientist

- Some are scientists first then clinician
- I need to simplify for patient and patient care.
- Science is great, but not good if there isn't a clinical application.
- Some lectures are science based without clinical application.
- My lecture will be a hybrid. Showing clinical applications of the science

It is wonderful to have someone who's juggling so many aspects of optometry [scientific, clinical experience, teacher & lecturer]. It is refreshing and very informative. -Sarah

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"The Comfort Zone"

Confidence
Capable
Courage
Commitment

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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 3	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*	roseola infantum	beta	Human herpesvirus 6*	roseola infantum	beta
Human herpesvirus 7	mononucleosis	beta	Human herpesvirus 7	mononucleosis	beta
Human herpesvirus 8	Kaposi's Sarcoma-associ.	gamma	Human herpesvirus 8	Kaposi's Sarcoma-associ.	gamma

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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
 - 11's not critical to determine HSV 1 or 2
 - Stromal keratitis
 - Endothelitis
 - Neurotrophic keratopathy
 - Serious complication

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73-year-old woman

- Tuesday, 11-22-2022
- CC: OD possible clogged tear duct
 - Itchy inner part of the eye
 - Referred by patient's Primary Care Physician
 - Thinks clogged tear duct or infection
- On Friday, 11-18-2022
 - OD started to bother patient
 - Tried Visine with little or no help
- Meds: Cardizem, Eliquis, Trelegy, and Albuterol
- VA: OD 20/80 OS 20/30
- IOP: OD 10 OS 15 1:17 pm


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Chat Box: Evaluation and Treatment



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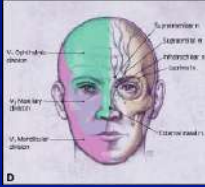
Let's Hear from the Patient



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Herpes Viruses are Classified by Their Location in the Latent State

Herpes Variant Type	Hosts	Latent Site	Target Cell Type	Latency	Characteristics
1	Herpes simplex 1 (HSV-1)	Alphaherpesvirinae	Mucocytotrophic	Neuron	Oral contact
2	Herpes simplex 2 (HSV-2)	Alphaherpesvirinae	Mucocytotrophic	Neuron	Oral contact, usually sexual
3	Varicella-Zoster virus (VZV)	Alphaherpesvirinae	Mucocytotrophic	Neuron	Control of respiratory tract
4	Epidemic Keratoconjunctivitis (EKC)	Gammaposvirinae	Epitheliocytotrophic	Epithelial	Direct, respiratory route
5	Cytomegalovirus (CMV)	Betaherpesvirinae	Epitheliocytotrophic and possibly lymphocytotrophic	Monocytes, lymphocytes and possibly other cells	Orbital, blood, hematogenous, and respiratory routes
6	Herpes Simplexvirus oculi	Betaherpesvirinae	Tropocytotrophic and others	Tropocytotrophic and others	Orbital, respiratory route
7	Human Herpesvirus 8 (HHV-8)	Betaherpesvirinae	Tropocytotrophic and others	Tropocytotrophic and others	Unknown
8	Herpesvirus saimiri (HVS-1) and Herpesvirus saimiri (HVS-2)	Gammaposvirinae	Epitheliocytotrophic	Macrophage	Exchange of body fluids



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Treatment 11-22-2022

- Herpes Simplex Keratitis x 7 lesions
 - Educated patient on finding
 - Photo and video documents
 - Valtrex 1000 mg PO TID
 - Watch closely
 - Prokera not covered by insurance, patient declined Prokera
 - Add steroid at sign of reversal
 - RTC 1 day for HSV keratitis check

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1 Day Follow UP 11-23-2022

- Feels slightly better
- VA: OD 20/70 OS 20/25
- Valtrex 1000 mg
 - * 3 times yesterday
 - * 2 today



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1 Day Follow UP 11-23-2022



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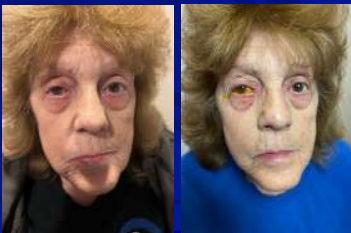
1 Day Follow UP 11-23-2022

- Improving
- Continue Valtrex 1000 mg PO TID
- Watch closely
- Photos and video documents
- Add steroids when reversal
- RTC in 2 days

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3 Day Follow Up Friday 11-25-2022

- Patient taking Valtrex as prescribed
- Reports watering over the last 2 days
- VA OD 20/70 OS 20/25
- IOP OD 11 OS 15



11-25-2022 11-23-2022

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3 Day Follow Up Friday 11-25-2022


Time for steroid?



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3 Day Follow Up Friday 11-25-2022

- Improving
- Responding to treatment
- Finish Valtrex PO
- Add Ioteprednol OD QID
- RTC 1 day, leaving town for weekend
- RTC Monday, gave patient my cell number



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6 Day Follow Up Monday 11-28-2022

- ~ Patient reports improvement since LOV
- ~ Still some watering
- ~ VA OD 20/70 OS 20/25
- ~ IOP OD 15 OS 16

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6 Day Follow Up Monday 11-28-2022

11-23-2022 11-25-2022 11-28-2022

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6 Day Follow Up Monday 11-28-2022

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6 Day Follow Up Monday 11-28-2022

- ~ HSV 7 lesions improving and responding well to treatment
- ~ Mild corneal haze
- ~ Cataract OD limiting vision
- ~ Finish Valtrex PO TID
- ~ Continue loteprednol OD QID
- ~ Recheck in 1 week

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13 Day Follow Up Monday 12-05-2022

- ~ Valtrex is finished
- ~ Loteprednol OD QID
- ~ Eye feels normal and no watering
- ~ VA OD 20/60 OS 20/25
- ~ IOP 14/14

12-05-2022 11-23-2022


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13 Day Follow Up Monday 12-05-2022

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13 Day Follow Up Monday 12-05-2022



- ~ 7 HSV lesions resolved
- ~ Cornea haze and irregular cornea surface
 - * Limiting BVA
- ~ Loteprednol OD BID until bottle is empty
- ~ RTC 1 month – consider cataract consult



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6 Week Follow Up Wednesday 1-04-2023

- ~ Valtrex and loteprednol finished
- ~ VA: OD 20/40 OS 20/25
- ~ IOP 15/15
- ~ Cornea haze minimum
- ~ No iritis
- ~ Nasal ectropion
- ~ Tx: refer for cataract eval

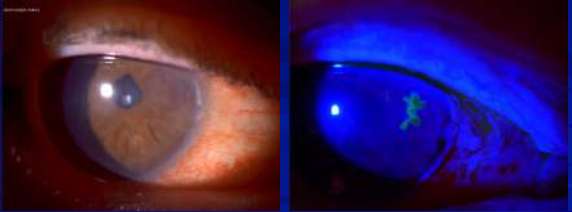
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72-year-old white man

- ~ First saw patient 6-26-2017
- ~ History of herpes viral keratitis and cataract OD
- ~ Wants opinion on keratitis and cataract
- ~ VA: OD 20/100 OS Prosthetic
 - * Saw at age 2 to OS
- ~ Valtrex PO 500 mg
- ~ Timolol OD QD
- ~ Prednisolone OD QD
- ~ IOP OD 18
- ~ **Diagnosis: Monocular patient**
 - * Ocular HTN/Steroid responder
 - Good IOP
 - * Recurrent HSV keratitis
 - Quiet
 - * Iritis
 - Quiet
 - * Cataract
 - Refer for cataract surgery went ready
 - Will increase Valtrex PO
 - * Cataract surgery 1-18-2018
 - Increased Valtrex pre and post op
 - VA: OD 20/25

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73-year-old white man



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73-year-old white man



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73-year-old white man



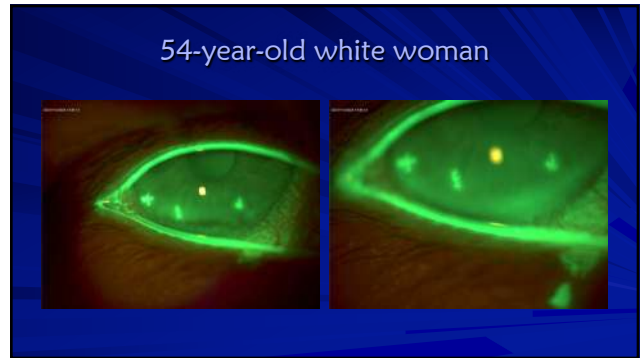
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54-year-old white woman

- Review of records of ECP: 12-30-2021 OD red, itch, - especially the inner corner
- PCP – ciprofloxacin 2 drops every 4 hours
 - Used for 2 days, no improvement
- Hurts into cheekbone
- Dx: cornea abrasion
- Tx: Maxitrol OD TID, check 1 week

- January 3, 2022 – patient wants 3rd opinion
- Eye started to improve over weekend, now redness and irritation is back
 - Not as itchy
 - Pressure when closes eyes

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Herpes Viruses are Classified by Their Location in the Latent State

Saw HSV cases now let's see Zoster

Herpes Latent Site	Name	Sub Family	Target cell type	Latency	Transmission
1	Herpes simplex 1 (HSV-1)	Alphaherpesvirinae	Mucosathelia	Neuron	Close contact
2	Herpes simplex 2 (HSV-2)	Alphaherpesvirinae	Mucosathelia	Neuron	Close contact, mostly sexual
3	Varicella Zoster virus (VZV)	Alphaherpesvirinae	Mucosathelia	Neuron	Contact or respiratory route
4	Epidemic Keratoconjunctivitis (EKC)	Gammaposvirinae	B lymphocytes, goblet cells	Static	Static
5	Cytomegalovirus (CMV)	Betaherpesvirinae	Epithelia, macrophages, lymphocytes, others	Macrophages, lymphocytes and dendritic cells	Contact, blood transfusion, breastmilk, congenital
6	Herpes lymphocytic choriomeningitis	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	Human herpes virus 9 (HHV-9)	Gammaposvirinae	Epithelial cells	Unknown	Contact of body fluids?

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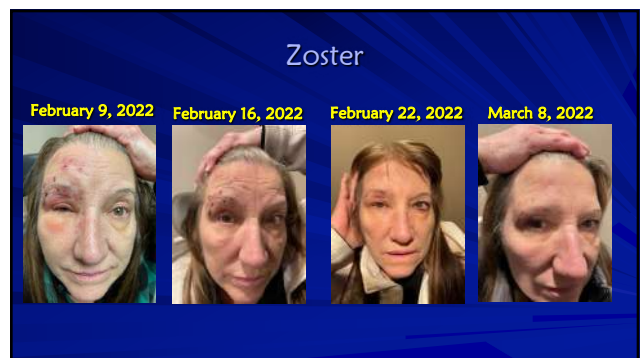
Varicella-Zoster Virus (VZV)

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

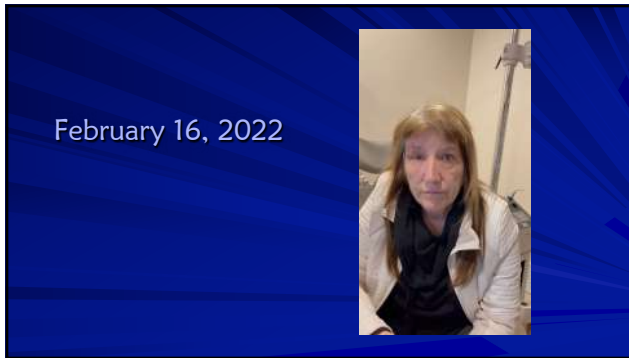
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Varicella-Zoster Virus (VZV)

~ The best time to diagnose and treat

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Varicella-Zoster Virus (VZV)

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

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24-48 hours before Zirgan arrives

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

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Herpes Simplex Virus Keratitis

- ~ Infectious epithelial keratitis
- ~ Stromal keratitis
- ~ Endotheliitis
- ~ Neurotrophic keratopathy

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Cryopreserved

Indications:

- PROKERA is intended for use in eyes in which ocular surface cells are damaged or underlying stroma is inflamed or scarred. Acting as a self-retaining biologic corneal bandage, PROKERA effectively treats superficial corneal surface diseases by suppressing inflammation and related pain, promoting epithelial healing, and avoiding haze.
- PROKERA is inserted between the eyeball and the eyelid to maintain space in the orbital cavity and to prevent closure or adhesions. Placement of the conformer also enables application of the cryopreserved amniotic membrane to the ocular surface without the need for sutures.
- PROKERA is for single-use only in one patient by an ophthalmologist or optometrist.

Contraindications:

- PROKERA should not be used in eyes with glaucoma drainage devices or filtering blebs.

Precautions:

Location & Temperature	Use After Storage
Unopened, isolated, airtight container	Within the expiration date printed on outer shipping box
-10°C to +10°C (14°F to 50°F) Example: ultra low temperature freezer, standard freezer, or standard refrigerator	Within the expiration date printed on product packaging, shelf life is 2 years from date of manufacturing

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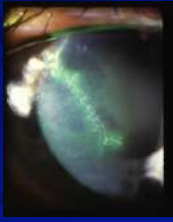
37-year-old woman
OD red and painful

Va	20	30	Current Correction
cc	/	20	R -2.50-1.00 x 180
			L -3.25-1.00 x 180

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

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Slit Lamp Evaluation



- ~ Diagnosis
- ~ Ocular history
 - * First episode
- ~ Treatment
- ~ Maintenance of oral antiviral?

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4 weeks later



- ~ Resolved
- ~ Chance of occurring again within 12 months?
 - * 25%

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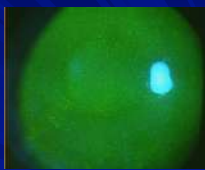

Cranium Keeper

~ Viroptic (trifluridine solution) should be used for how long?

- * One drop every 2 hours while awake (up to 9 drops per day)
- * 21 days via package insert/instructions

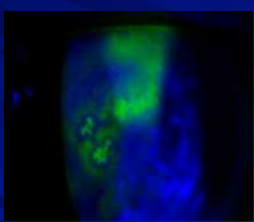
~ Zirgan (ganciclovir ophthalmic gel) 0.15%

- * One drop five times per day until the corneal ulcer heals
- * Then one drop three times per day for seven days

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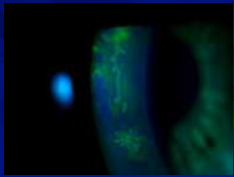
Slit Lamp Evaluation



- ~ 5 months later
- ~ Treatment
- ~ Maintenance of oral antiviral?
 - * Education patient on treatment options
 - 43% occurring again

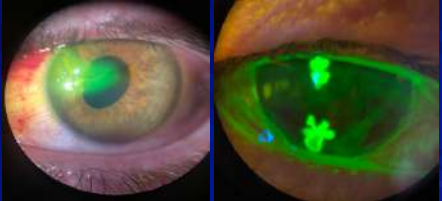
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4 Months Later



- ~ Ocular history
 - * Third episode
- ~ Treatment
 - ~ Oral antiviral maintenance?
 - * What dosage?
 - Short term
 - Long term

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Herpetic Eye Disease Study

- HEDS I
 - Benefit from steroids in stromal keratitis
 - No benefit from oral Acyclovir in stromal keratitis
 - Benefit from steroids if iritis present
- ~ HEDS II
 - * No benefit from Acyclovir to stop progression to stromal or iridocyclitis
 - * Maintenance dose 400 mg BID, decreases recurrence by 41% within 1st year

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Recurrent Herpes Simplex Keratitis

- ~ Treatment
 - * Topical antiviral
 - * Oral antiviral
- ~ Remember to check for?
 - ~ Patient is allergic to Penicillin and Keflex
 - ~ Patient is also 2 months pregnant

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Medical History

~ Before we Rx any medications we take a thorough *medical* history which includes:

- CC
- HPI
- ROS
 - Kidney disease, liver disease, dialysis
- PFS History
- Current Medications
- Allergies...Adverse Reactions/Allergies
- Pregnancy...any chance you might be pregnant?

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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 outweigh 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
 - o Disease-associated maternal and/or embryo/fetal risk- omit if not applicable
 - o Dose adjustments during pregnancy and the postpartum period - omit if not applicable
 - o Maternal adverse reactions - omit if not applicable
 - o Fetal/Neonatal adverse reactions- omit if not applicable
 - o Labor or delivery - omit if not applicable
 - * Data- omit if none of the headings are applicable
 - o Human Data - omit if not applicable
 - o 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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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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Oral Anti-Virals

- ~ 3rd generation, go into every cell but only activate in viral infected cells
 - * (1st generation=mutagenic)
- ~ Use prophylactically prior to PKP, LASIK and PTK

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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 Novartis 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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- Treatment
 - Zirgan 0.15%
 - Caution Zirgan and Viroptic are Category C
 - Steroid
 - Artificial tears
 - Valtrex
 - 1000 mg TID PO
 - 500 mg QD PO
 - Add/consider L-Lysine

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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 VIREX
 EYE DISEASE
 The Herpes Eye Disease Study Group | N. Engl. J. Med. 1988;319:200-6

- ~ 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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Acyclovir vs. Valacyclovir vs. Famciclovir

What is the difference?

Acyclovir

Zovirax® contains lactose

Presence or absence of lactose in generic acyclovir varies

Valacyclovir

Valtrex® and all generics are free of lactose

Famciclovir

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

Famciclovir ophthalmic gel

Oral antivirals:

- Acyclovir
- Valacyclovir
- Famciclovir

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The deeper the involvement, the more efficacious orals become. But what about epithelial keratitis?... There seems to be equivalence

Oral acyclovir (Zovirax) in herpes simplex dendritic epithelial keratitis

60 patients with HSV dendritic ulceration included in 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!

Cochrane Database Syst Rev 2008;8(2):1-196

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Lysine or L-Lysine

- An essential amino acid
- It is necessary for human health
- But the body can't manufacture it
- You have to get lysine from food or supplements
- Amino acids like lysine are the building blocks of protein
 - Lysine is important for proper growth

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Lysine and Herpes

- Some studies have found that taking lysine on a regular basis may help prevent outbreaks of cold sores and genital herpes
- Lysine has antiviral effects by blocking the activity of arginine
 - Which promotes HSV replication
- One review found that oral lysine is more effective for preventing an HSV outbreak than it is at reducing the severity and duration of an outbreak
- One study found that taking lysine at the beginning of a herpes outbreak did not reduce symptoms.
- Typically comes in 500 mg
 - 2000-3000 mg while active or infectious
 - 1000 mg as maintenance

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Cranium Keeper

- Percentages in HSV keratitis
 - * 25%
 - * 43%
 - * 41%

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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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Prevention Through Vaccination

- How effective are today's vaccines?
- Zostavax (Merck)- subcutaneous injection
 - * Does not confer life-long immunity ... effect wanes after 5 years with booster suggested at 10 years
 - * 38-70% reduction in risk of shingles after vaccination
 - * 60-70% reduction in occurrence of PHN
 - * Not recommended for patients with post-HZV corneal or intraocular infection
 - * Patients with previous shingles may experience ocular, dermatologic, or disseminated disease
- Shingrix- Subunit Vaccine HZ/su (GSK)- Intramuscular 2 injections
 - * Recombinant VZV glycoprotein E with AS01B adjuvant system
 - * Primary vaccine with second dose 2 months later
 - * ZOE-50 trial reduced risk of shingles by 97% (Cunningham, et al NEJM 2016)
 - * ZOE-70 trial reduced risk of shingles by 90% (Cunningham, et al NEJM 2016)
 - * Pooled data demonstrated HZ/su associated risk reduction of PHN by 89%
 - * Potentially beneficial for immunocompromised individuals

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Serious Complications of Herpetic Eye Disease

- Neurotrophic States
- Acute Retinal Necrosis
- Post Herpetic Neuralgia

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Post Herpetic Neuralgia

How To Treat and Possibly Avoid It

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Post Herpetic Neuralgia (PHN)

- Patients with PHN report decreased quality of life and interference with activities of daily living
- Approximately 1 million cases of herpes zoster occur annually in the US
 - * One in every three people develops herpes zoster during their lifetime
- PHN is a frequent complication occurring in 5% to 15% of cases
 - * Causing moderate to severe neuropathic pain
- PHN is a neuropathic pain syndrome characterized by pain that persists for months to years after resolution of the herpes zoster rash
- Neuropathic pain
 - * Does not respond consistently to classic non-opioid analgesic drugs
 - * Better treated with antidepressant, anticonvulsant drugs and topical agents
- Neuropathic pain is a major public health problem worldwide
 - * Unclear mechanism
 - * Treatment is one of the most difficult medical problems

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Post Herpetic Neuralgia (PHN) Treatment

- ~ Approaches to management of post herpetic neuralgia include
 - * Preventing herpes zoster through vaccination and/or antiviral treatment
 - * Administering specific medications to treat pain
- ~ First-line drugs
 - * Anti-convulsant -neuropathic pain
 - Calcium channel α2-δ ligands
 - gabapentin (Neurontin) and pregabalin (Lyrica)
 - * Tricyclic antidepressants
 - amitriptyline, nortriptyline, desipramine
 - * Topical lidocaine patches
 - Works because PHN is a peripheral neuropathy
 - **Radicular pain** is a type of **pain** that radiates into the lower extremity directly along the course of a spinal nerve root (topical lidocaine not effective)

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Lyrica - pregabalin Neurontin - gabapentin

- ~ Does Duration of Neuropathic Pain Impact the Effectiveness of Pregabalin?
 - * Patients with chronic pain conditions such as neuropathic pain frequently experience delays in diagnosis and treatment
 - * Pregabalin significantly improves pain irrespective of the length of time since onset of neuropathic pain

Pharmaceuticals 2016 Sep 2; doi: 10.1111/jcpp.12445 Does Duration of Neuropathic Pain Impact the Effectiveness of Pregabalin? | [View Article](#) | [View Full Text](#) | [References](#) | [Citations](#) | [Metrics](#) | [Permissions](#) | [Share](#)

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Neurotropic Cornea Ulcer

- ~ Difficult to manage due to:
 - * Decreased ocular innervation
 - * Decreased tears production
- ~ Medications to avoid
 - * Topical corticosteroids
 - May increase collagenase activity and promote stromal melting
 - * Topical NSAIDs
 - No shown benefit in wound healing
 - Can decrease corneal sensitivity

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Neurotropic Cornea Ulcer

- ~ Traditional Treatments
 - * Preservative-free artificial tears, gels, and ointments
 - * Discontinuation of any topical ocular therapies
 - Those that can decrease corneal sensitivity
 - timolol, betaxolol, sulfacetamide, diclofenac, ketorolac
 - Those that contain preservatives
 - * Punctal occlusion
 - * Doxycycline 100 mg PO qd/qod; anti-inflammatory properties
 - * Autologous blood serum
- ~ Alternative to traditional treatments
 - * Scleral contact lenses
 - * Amniotic Membrane

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Oxervate™ (cenegermin-bkbj)

- ~ Approved 2018 (August 28, 2018)
- ~ Dompe farmaceutici SpA
- ~ Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- ~ Dosing: Instill 1 drop in affected eye 6 times per day (at 2-hour intervals) for 8 weeks
 - * Used as eye drop
 - Not infused or injected
- ~ Storage issues: in the freezer at the pharmacy
 - * Patient keeps the individual vials in the fridge – once "actively ready" for use, then it is only stable for 12 hours
- ~ Contraindications
 - * None

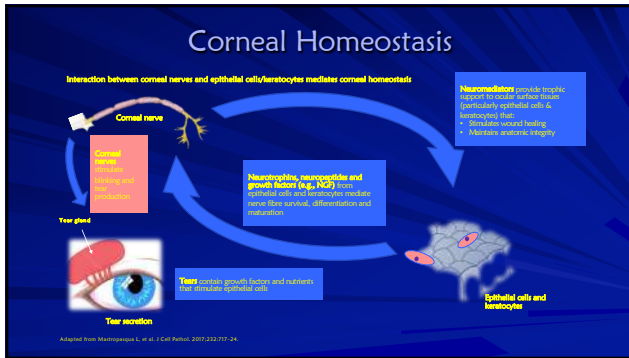
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Escherichia Coli

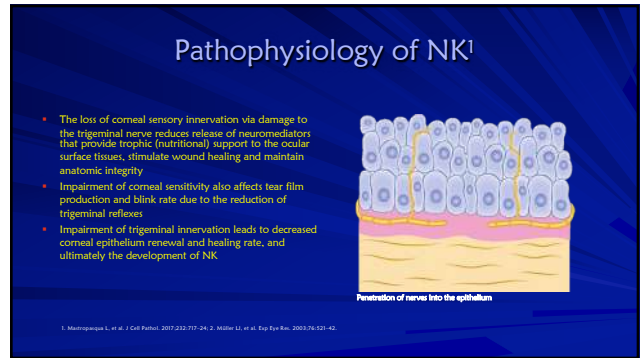


Escherichia coli produced in the lab's kitchen. Image courtesy of iStock.

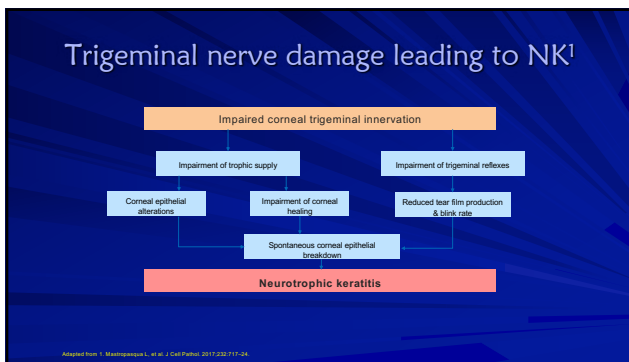
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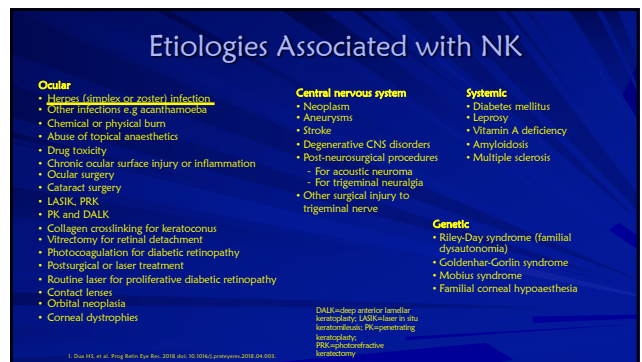
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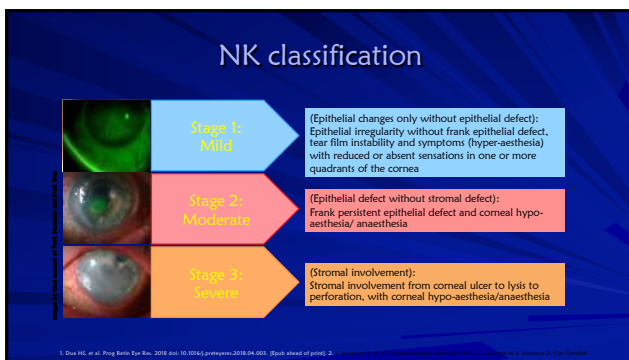
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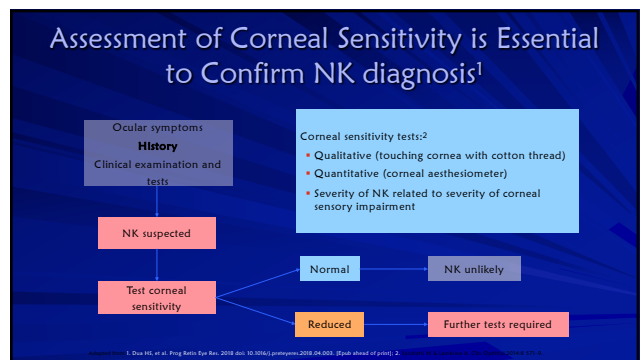
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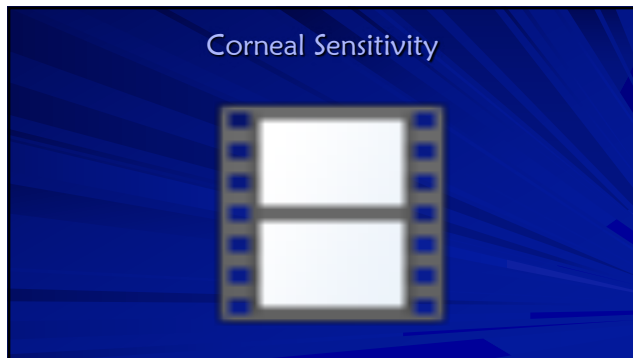
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Endogenous NGF maintains corneal integrity by three mechanisms

Endogenous Nerve Growth Factor acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e., p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity!

CORNEAL INNERVATION

NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves^{2,3}

CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells⁵

TEAR SECRETION

NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion^{1,4}

SHOWN IN PRECLINICAL MODELS:

1. Morigiwa M, Morigiwa Y, Nishida H, Saito M, Yoshida M. Understanding the pathogenesis of neuropathic keratitis: the role of nerve growth factor. *Cornea*. 2013 Apr;32(4):529-34. 2. Mollnes CD, Skjelvåg A, Tjønn A. Corneal sensory innervation, corneal and lacrimal gland function. *Acta Otolaryngol Scand*. 2001;127(4):463-70. 3. Saito M, Yoshida M. Regrowth and reorganization of peripheral sensory C-fiber afferents in the rat cornea. *Invest Ophthalmol Vis Sci*. 2001;42(11):3438-44. 4. Mollnes CD, Skjelvåg A, Tjønn A. Corneal Sensory Innervation, Corneal and Lacrimal Gland Function. *Acta Otolaryngol Scand*. 2001;127(4):463-70. 5. Morigiwa M, Morigiwa Y, Nishida H, Saito M, Yoshida M. Understanding the pathogenesis of neuropathic keratitis: the role of nerve growth factor. *Cornea*. 2013 Apr;32(4):529-34.

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Active ingredient structurally identical to human nerve growth factor produced in ocular tissues

- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons!
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s!
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein!

1. Saito M, Nishida H, Morigiwa Y, Yoshida M, Morigiwa M. Topical treatment with nerve growth factor for corneal neuropathic keratitis. *Invest Ophthalmol Vis Sci*. 2011;52(16):5748-52. 2. Yoshida M, Nishida H, Saito M, Morigiwa Y, Morigiwa M. Regrowth and reorganization of peripheral sensory C-fiber afferents in the rat cornea. *Invest Ophthalmol Vis Sci*. 2001;42(11):3438-44.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- OXERVATE™ is supplied in a weekly carton containing 7 multiple-dose vials*
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares

*Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) (15 package insert), Boston, MA, Dompag U.S., Inc., 2018.

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Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues

Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues

1. Saito M, Nishida H, Morigiwa Y, Yoshida M, Morigiwa M. Topical treatment with nerve growth factor for corneal neuropathic keratitis. *Invest Ophthalmol Vis Sci*. 2011;52(16):5748-52.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Dosing and Administration

Instill 1 drop of OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

2 Every 2 hours

6 Apply 6 times daily

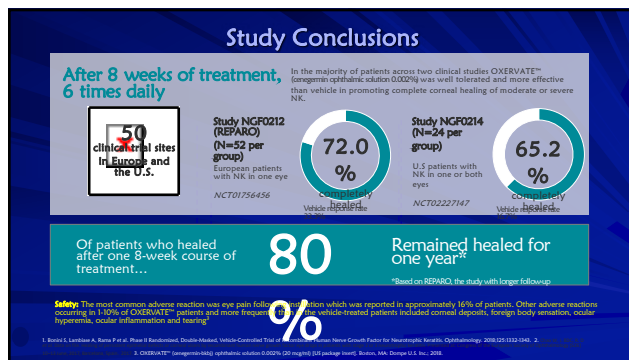
8 Continue for 8 weeks

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) (15 package insert), Boston, MA, Dompag U.S., Inc., 2018.

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OXERVATE™ (cenegermin-bkbj)

- Adverse reactions: very well tolerated
- The most common adverse reaction in clinical trials
 - eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears
- Contact lenses (therapeutic or corrective) should be removed before applying cenegermin
 - presence of a contact lens may limit the distribution of cenegermin-bkbj onto the corneal lesion
 - Lenses may be reinserted 15 minutes after administration.

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Oxervate™ (cenegermin-bkbj)

- Approved 2018
- Dompé pharmaceutical SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- Dosing: Instill 1 drop in affected eye 6 times per day (at 2 hour intervals) for 8 weeks
- Storage issues: in the freezer at the pharmacy; patient keeps the individual vials in the fridge – once “actively ready” for use, then it is only stable for 12 hours
- ADRs: eye pain, inflammation, corneal deposits

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Sutureless Amniotic Membrane

- Amniotic membrane is the innermost lining of the placenta (amnion)
 - Shares the same cell origin as the fetus
 - Stem Cell behavior
- Regenerative platform that possesses natural growth factors and scaffolding properties that are
 - Anti-inflammatory
 - Anti-scarring
 - Anti-angiogenic
- Therapeutic action
 - Promotes Stem Cell Expansion
 - Suppresses pain
 - Promotes cellular migration
 - Expedites recovery

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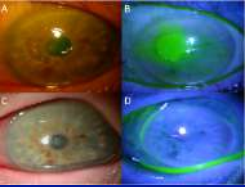
Cryopreserved and Dehydrated

- Cryopreserved
 - PROKERA- Biotissue
- Dehydrated
 - AmbioDisk -IOP Ophthalmics
 - BioDOptix – BioD
- Taped tarsorrhaphy/tapesorrhaphy

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67-year-old woman with a history of recurrent HSV keratitis and dry eye

- She presented with mild ocular discomfort (cornea hypoesthesia) and progressive decrease of vision (20/400) for several weeks
- Examination revealed a central corneal epithelial defect surrounded by a rim of loose epithelium, stromal edema, and anterior chamber inflammatory reaction (Fig. A, B)
- Neurotrophic keratitis



- PROKERAB was placed along with punctal plug, tapeorrhaphy, and oral Acyclovir
- Complete healing occurred within one week, resulting in clear cornea, 20/20 vision, and improved tear meniscus (Fig. C, D).

Early intervention with PROKERAB promotes regenerative healing and prevents haze

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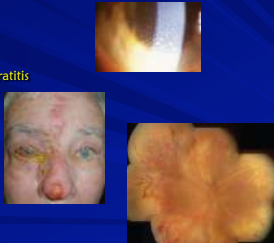
Severe Neurotrophic Keratopathy

- May need surgical repair
 - Lamellar keratoplasty
 - Penetrating keratoplasty
 - Sutured multilayer amniotic membrane transplantation
 - Used in defects as deep as 90% of the depth of the stroma
 - Cyanoacrylate glue with a soft bandage contact lens
 - Defects smaller than 2 mm

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Ocular Findings Associated with Herpes Family

- Episcleritis
- Scleritis
- SPK
- Pseudodendritic keratitis
- Stromal keratitis
- Uveitis
- Irish atrophy
- Glaucoma
- Vitritis
- Retinitis
- Choroiditis
- Optic neuritis
- CN palsy



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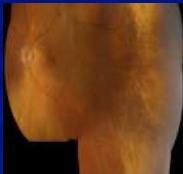
Acute Retinal Necrosis (ARN)

- A rare presentation of herpetic or other viral disease
 - Varicella zoster is most common cause
 - HSV 1-2, CMV, EBV infections
- Characterized by large areas of retinal whitening and necrosis that spreads centripetally with a high rate of accompanying detachment and vascular occlusion
- Historically, ARN was believed to affect healthy adults
 - Increasing evidence suggests that patients who develop ARN have underlying immune dysfunction
- Polymerase chain reaction-based (PCR) analysis of the intraocular fluid is valuable in diagnosis of infectious retinitis
 - Aqueous or vitreal fluid
 - Small sample volume from the anterior chamber is usually sufficient to detect copies of VZV, HSV, CMV, or Toxoplasmosis gondii DNA in patients with infectious retinitis
 - Results within 1 week

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Acute Retinal Necrosis (ARN)


- HIV uninfected patients
 - VZV greater than 50%
 - HSV-1 and HSV-2
 - CMV, less common
- Patient with HIV
 - VZV 33%
 - CMV then HSV-1/HSV-2



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PORN

- Progressive Outer Retina Necrosis (PORN)
 - Starting in posterior pole then outer retina
 - ARN emphasis is peripheral retina
 - Severely immunosuppressed patient
 - HIV positive patient
 - Minimal vitreous involvement despite extensive retina involvement
- It is documented herpetic retinitis can affect any part of the retina
 - Regardless of immune status



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Treatment


- ~ Oral valacyclovir at 2 g TID can achieve systemic levels similar to intravenous acyclovir
- ~ Intravenous acyclovir 10-15mg/kg TID for 5-10 days followed by oral regimen for 6-12 weeks
- ~ Intra-vitreous injection of foscarnet or ganciclovir can be considered
- ~ Laser photocoagulation is controversial
- ~ Management of the retina detachment is both tractional and rhegmatogenous
 - * Vitreous condensation and inflammation
 - * PVR occurs in up to 75% of patients with ARN

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Differential Diagnosis

- ~ Necrotizing retinitis is typically from Herpes Family of viruses but keep in mind:
 - * Syphilitic retinitis
 - * Toxoplasmic retinochoroiditis
 - * Primary vitreo-retinal lymphoma
 - * Sarcoidosis
 - * Tuberculosis
 - * Toxocariasis
 - * Fungal or bacterial retinitis/endophthalmitis
 - * Behçet's disease

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Questions and Thank You!

Herpes A to Z for the Eye Care Provider

Greg Caldwell, OD, FAAO
Primary Eye Care Conference
Pittsburgh

Optometric Education Consultants
Saturday, February 17, 2024



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