

Comfortably Numb... Management of Neurotrophic Keratitis

Brandon Ayres, MD
Co-Director of Cornea Fellowship, Wills Eye Hospital – Cornea Service

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Director of Specialty Contact Lenses, Wills Eye Hospital – Cornea Service

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Disclosures – Brandon Ayres, MD

- Alcon (C, S)
- Allergan (C, S)
- Glaukos (C)
- Bausch ad Lomb (C)
- Dompe (C, S)
- Eyevance (C)
- Eye Point (C)
- Gore Surgical (C)
- Kala(C)
- Omeros (C)
- Microsurgical Technology (C)
- Sight Sciences (C)
- Tear Lab (C, S)
- Tarsus (C)
- Zeiss (C)

*C = Consultant
*S = Speaker Bureau

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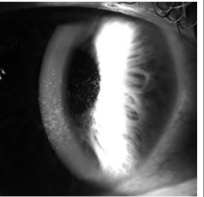
Disclosures – Clark Chang, OD, MS, FAAO

- Employment Disclosure
 - Wills Eye Hospital, Cornea Service – Director, Specialty Contact lenses
 - Glaukos - Medical Affairs Manager
- Other Disclosures (Speaker Bureau/Ad Board)
 - Allergan
 - Eyeovia
 - Visus Therapeutics
 - Dompe Pharmaceutical
 - Oculus

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A Real-World Case – Unresponsive Dry Eyes

- 50 YO female c/o blurry & fluctuating VA, mild scratchiness (OD>OS) & photophobia
 - LASIK OU ~21 Mth ago (03/2017) with Flap-lift enhancement in OD (06/2017)
 - As per Pt - No Hx of DED, symptoms onset post-LASIK & Dx with Dry Eyes
 - Hx of SCL wear x 35 Yrs
 - IDDM x 10 Yrs, not well controlled (A1C~8.7)
- Current Treatments
 - Tried several OTC ATs/Gels/UNGS – “They Don’t Help”
 - Currently using Refresh Mega 12-15x/Day, OU
 - Does not recall being Rx’ed any topical medications
 - No other auxiliary therapies (Warm compress, lid hygiene, et c)

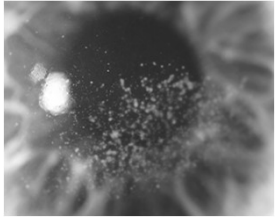


Case Courtesy By Scott Hauswirth, OD, FAAO

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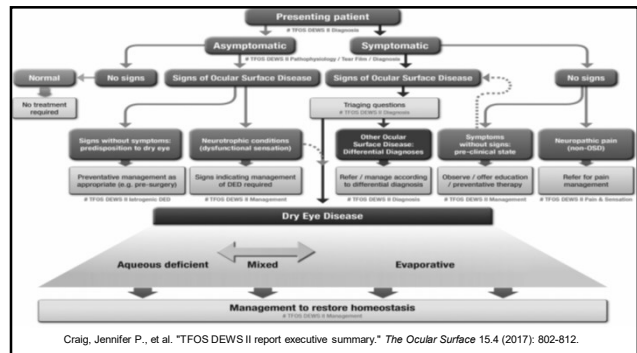
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 - BCVA: OD 20/40 OS 20/40-2
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 - TBUT: 4 sec OD, 5 sec OS
 - Lids: 12/15 turbid OD, 10/15 turbid OS (good volume OU)
 - Conj: (-) LG stain OU
 - Cornea: 2-3+ PEK in central flap zone OD, 2+ PEK in central flap zone OS
 - Sub-epithelial opacities did pick up NaFL stain!



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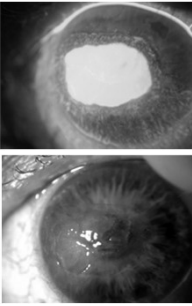
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What is NK?

- Neurotrophic keratitis (NK) is a degenerative disease characterized by
 - Corneal sensitivity reduction
 - Spontaneous epithelium breakdown
 - Impaired corneal healing
- Development of
 - Corneal ulceration
 - Melting
 - Perforation



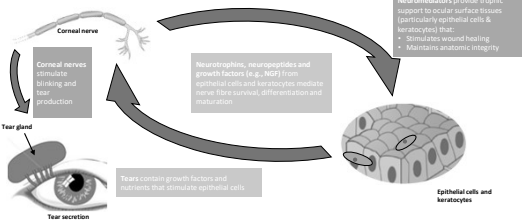
longstanding PKD
Image credit: Lynette Jöhri, MD

Sachithri M, Lambiasi A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;8:571-579. Published 2014 Mar 28. doi:10.54002/COP.4492

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Corneal homeostasis

Interaction between corneal nerves and epithelial cells/keratocytes mediates corneal homeostasis

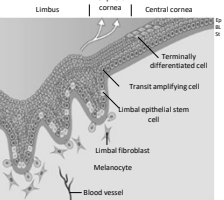


Adapted from Mastroianni L, et al. J Cell Physiol. 2017;222:217-24

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Corneal epithelial cells

- Corneal integrity and function depends on a constant replenishment of epithelial cells
- Limbal stem cells divide asymmetrically to produce
 - Additional stem cells
 - Epithelial cells as they migrate out of the limbus
- Corneal epithelial cells and keratocytes regulate the survival, differentiation and maturation of nerve fibers
 - Release neurotrophins
 - Release growth factors



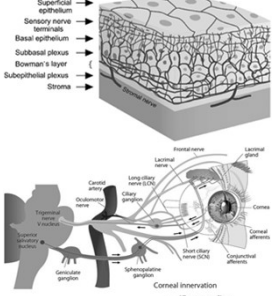
Ep. epithelium, 80. Bowman's layer, 70. stroma. Adapted from J. Steinbock. Available at: http://www.eyeweb.org/whats/08/08.html. Accessed July 2016.

Mastroianni L, et al. J Cell Physiol. 2017;222:757-24. Adapted from Shaheen B, et al. Surv Ophthalmol. 2014;59:263-85. doi:10.1016/j.surv.2014.05.001

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Corneal innervation

- Healthy cornea
 - Avascular
 - Extremely sensitive to pain¹
- Corneal sensory nerves originate from ophthalmic branch of the fifth cranial nerve¹
- Trigeminal nerve bundles lose perineurium and myelin sheaths where they enter the corneal stroma at the corneoscleral limbus^{1,2}
 - Why the cornea is transparent!

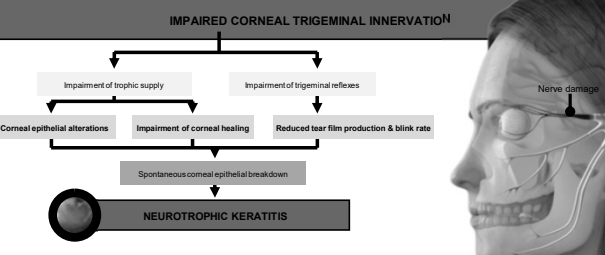


1 Mastroianni L, et al. J Cell Physiol. 2017;222:757-24. 2 Miller LU, et al. Exp Eye Res. 2002;76:123-42. 3 Quarr KL, et al. Prog Retin Eye Res. 2018; doi: 10.1016/j.preteyres.2018.04.009. (Epub ahead of print). 4 Shaheen B, Steinbock J. Epithelium: A Cell Biology of the Eye. Corneal Innervation. Clin Ophthalmol. 2014;8:571-579. Published 2014 Mar 28. doi:10.54002/COP.4492

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Nerve Malfunction: Central to NK


IMPAIRED CORNEAL TRIGEMINAL INNERVATION



Mastroianni L, Mastroianni-Giordano G, Nishii M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. J Cell Physiol. 2017;222(4):717-24.

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Diagnosing NK – History is Where It All Begins




OCULAR	SYSTEMIC	CNS
<ul style="list-style-type: none"> • Herpes (Zoster/Simplex) infection • Other infections, i.e. acanthamoeba • Chemical or physical burn • Drug toxicity, i.e. Chronic Glaucoma gtt Tx or Anaesthetic gtt abuse • Chronic ocular surface injury or inflammation • Ocular surgery <ul style="list-style-type: none"> • Cataract surgery, LASIK, PRK, PKP, DALK, CXL, Vitrectomy for RD, Photocoagulation for diabetic retinopathy • Contact lenses • Orbital neoplasia • Corneal dystrophies 	<ul style="list-style-type: none"> • Diabetes mellitus • Leprosy • Vitamin A deficiency • Amyloidosis • Multiple sclerosis 	<ul style="list-style-type: none"> • Neoplasm • Aneurysms • Stroke • Degenerative CNS disorders • Post-neurosurgical procedures <ul style="list-style-type: none"> - For acoustic neuroma - For trigeminal neuralgia • Other surgical injury to trigeminal nerve
	<ul style="list-style-type: none"> • GENETIC <ul style="list-style-type: none"> • Riley-Day syndrome (familial dysautonomia) • Goldenhar-Gorlin syndrome • Mobius syndrome • Familial corneal hypoesthesia 	

L. Quarr HS, et al. Prog Retin Eye Res. 2018; doi: 10.1016/j.preteyres.2018.04.009

13

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J. Dua HS, et al. Prog Retin Eye Res. 2018;doi:10.1016/j.pretevis.2018.04.003

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Variability of NK

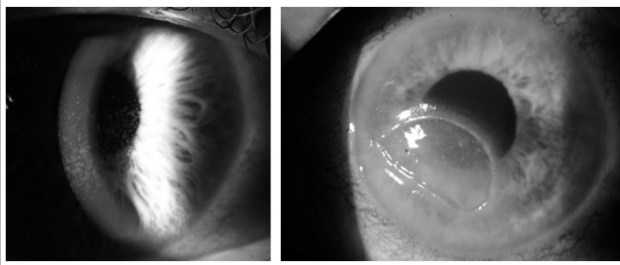
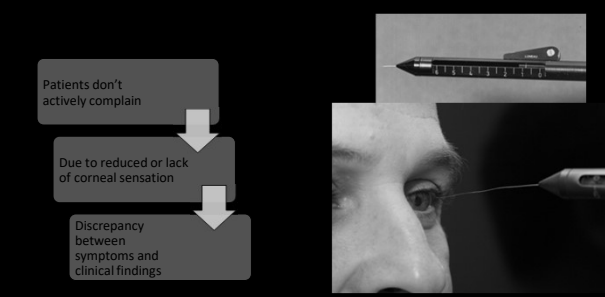


Image Courtesy, Scott Hauswirth, OD, FAAO

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Patients don't actively complain


↓

Due to reduced or lack of corneal sensation

↓

Discrepancy between symptoms and clinical findings

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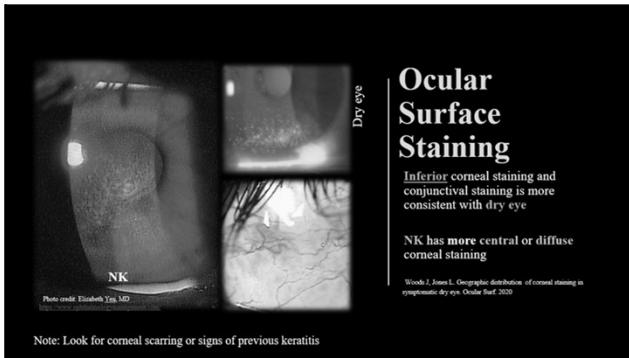


Severe PEK or Epithelial defect with disproportional ocular symptoms is highly suspicious of NK ie, corneal anesthesia

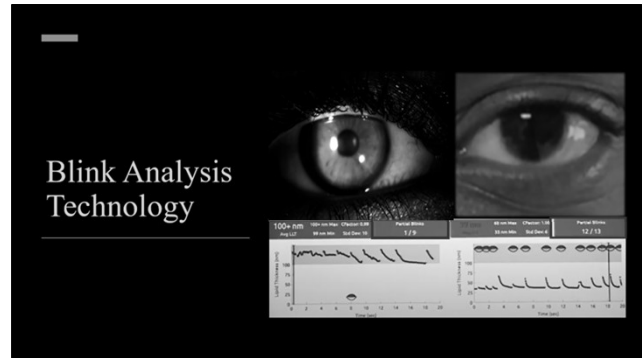
Symptoms

Stain without pain
Blur with stain
OR
Symptoms disproportionately less than the signs

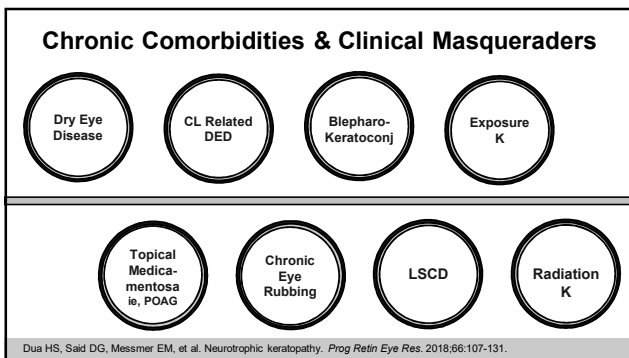
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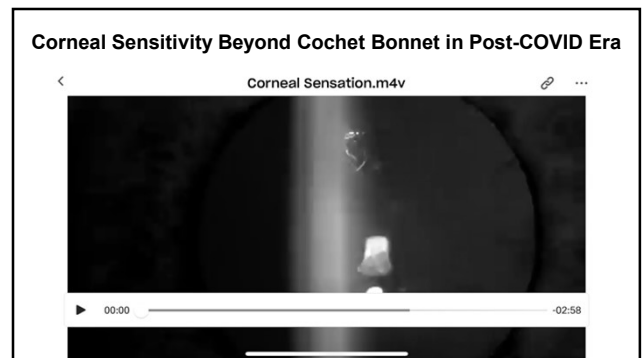
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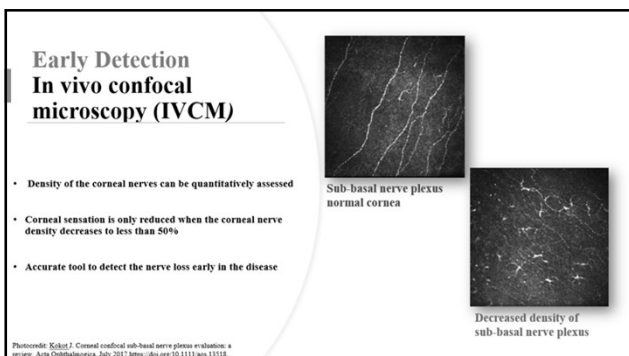
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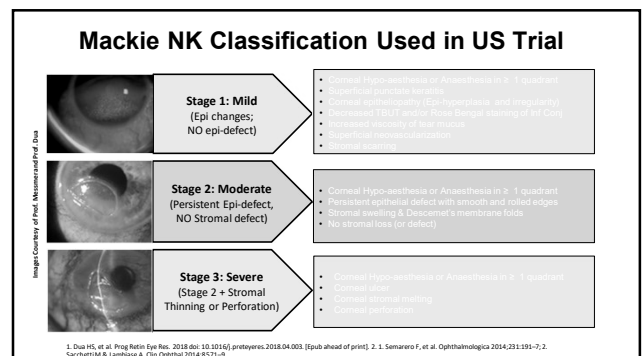
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NK IS A PROGRESSIVE DISEASE WITH TREATMENT GOALS AT EACH STAGE TO PREVENT PROGRESSION^{1,2}

If left untreated, NK can progress to a more severe stage²

STAGE 1 Mild²

- Improve epithelial quality and transparency
- Avoid epithelial breakdown

STAGE 2 Moderate²

- Prevent stromal involvement and corneal ulcer formation
- Promote corneal healing

STAGE 3 Severe²

- Stop stromal melting
- Prevent perforation that could lead to potential vision loss

1. Senzaki T, Ghanbarova G, Pellegrini M, Saitani S, Campos EC. Neurokeratic keratitis: current challenges and future prospects. *Exp Opin* 2018;10(3):45. 2. Dua HS, Sait DG, Meester EM, et al. Neurokeratic keratitis. *Prog Retin Eye Res* 2016;66:107-131.

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NK Treatment Options: NK Staging

Stage 1: Punctal Plugs, BSCL, Autologous serum tears, Amniotic membrane, Corneal neurotization

Stage 2: Remove offending agents, PFAT, Doxycycline, Tarsorrhaphy

Stage 3: Corneal neurotization, Scleral Lens, Glue, Corneal transplant

Steroids for any stage if underlying inflammation present

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NK Treatment Options: Tx Category

Treatments are typically used according to NK stage/severity but are not mutually exclusive of one another. The table is not an exhaustive list of all available treatment options.

Topicals	In-Office Procedures	Surgical Intervention
<ul style="list-style-type: none"> • Artificial tears • Corticosteroids • Autologous serum eye drops • Antibiotics • OXERVATE (cenegermin-bkbf ophthalmic solution 0.002% [20 mcg/mL]) 	<ul style="list-style-type: none"> • Therapeutic contact lenses • Punctal occlusion • Non-surgical eyelid closure • Amniotic membranes • Tissue adhesives 	<ul style="list-style-type: none"> • Tarsorrhaphy • Conjunctival flap • Corneal transplant • Direct neurotization • Sutured AMT

1. Dua HS, Sait DG, Meester EM, et al. Neurokeratic keratitis. *Prog Retin Eye Res* 2016;66:107-131. 2. Meester EM, Sait DG, Senzaki T, et al. Neurokeratic keratitis: the role of corneal nerves. *J Cell Physiol* 2017;207:717-724. 3. Senzaki T, Pellegrini M, Saitani S, et al. Neurokeratic keratitis: diagnosis and management. *Am J Ophthalmol* 2018;193:107-115.

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Dana et al Published a Consensus Paper that Included Recommendations on when to Test Corneal Sensitivity

Corneal Sensitivity Testing was Strongly Recommended when:

- Persistent epithelial defect that does not improve within 14 days
- Painless newly observed epithelial defect of unknown etiology
- History of herpetic eye disease
- History of procedures that might have damaged the trigeminal nerve or conditions that might have involved the trigeminal nerve
- Pain in the affected eye and multiple, concurrent risk factors, such as persistent poorly controlled diabetes and either reduced blink or a history of corneal procedures

The panel's guidance for when to conduct corneal sensitivity testing to screen for NK aligns with known NK etiologies

Dana R, Nishida K, Gupta N, et al. Expert consensus on the classification, diagnosis, and treatment of neurokeratic keratitis. *MOJ Ophthalmol* 2021;16(3):202-207.

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A Real-World Case – Unresponsive Dry Eyes

- 50 YO female c/o blurry & fluctuating VA, mild scratchiness (OD>OS) & photophobia
 - LASIK OU ~21 Mth ago (03/2017) with Flap-lift enhancement in OD (06/2017)
 - As per Pt - No Hx of DED, symptoms onset post-LASIK & Dx with Dry Eyes
 - Hx of SCL wear x 35 Yrs
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- Current Treatments
 - Tried several OTC ATs/Gels/UNGs – “They Don’t Help”
 - Currently using Refresh Mega 12-15x/Day, OU
 - Does not recall being Rx’ed any topical medications
 - No other auxiliary therapies (Warm compress, lid hygiene, etc)

Case Courtesy By Scott Hauswirth, OD, FFAO

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A Real-World Case – Unresponsive Dry Eyes?

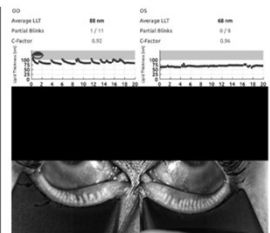
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 - Conj: (-) LG stain OU
 - Cornea: 2-3+ PEK in central flap zone OD, 2+ PEK in central flap zone OS
 - Sub-epithelial opacities did pick up NaFL stain!

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A Real-World Case – Unresponsive Dry Eyes?

- 50 YO female c/o blurry & fluctuating VA, mild scratchiness (OD>OS) & photophobia
- LipView: LLT: 88nm OD, 78nm OS (Arita grade 2 OU)
- Osmolarity: 303mOsm OD, 299mOsm OS
- Corneal sensitivity OU via Cotton-wisp
 - NO PRIOR ANESTHESIA!
 - Tested in flap zone only
 - Reduced sensitivity noted OU (-2 OU)
- Stage 1 (mild) NK
 - Confocal microscopy OU also ordered

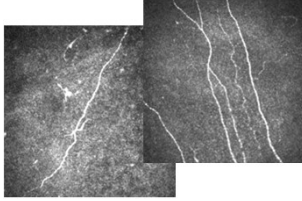


Case Courtesy By Scott Hauswirth, OD, FAAO

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A Real-World Case – Neurotrophic Keratitis (NK)

- Stage 1 (mild) NK
 - Confocal microscopy OU also ordered
 - Pt ed on NK risk factors (ie, IDDM, post-Op) + the importance of trophic factors in regulating tear production, epithelial health & wound healing
- Management
 - Autologous Serum 50% QID OU x 12 months
 - Warm compress, ATs
 - Mild improvement after 6 Mths, so decided to add Cenergermin 0.005%



(Baseline IVCM: Highest density NFL of 104 images)

Case Courtesy By Scott Hauswirth, OD, FAAO

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A Real-World Case – Pt's NK Tx Summary

- Slight improvement in PEK and vision to 6 months of ASEDs
 - OD: 20/40, 2-3+ central PEK
 - OS: 20/30, 2+ central PEK
- Addition of cenergermin (end of 8 weeks)
 - OD: 20/30+, 2+ central PEK
 - OS: 20/20, clear cornea
- 2nd round of cenergermin for OD only (end of 2nd 8 weeks)
 - OD: 20/15-1, clear cornea
 - OS: 20/15, clear cornea

Case Courtesy By Scott Hauswirth, OD, FAAO

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Autologous Serum Eye Drops (ASEDs)

- Non-allergenic, non-preserved drops derived from blood serum
- Concentration ranges from 20% to 100%
- Contains components such as EGF, vitamin A, TGFβ, neuropeptides
- Can induce proper proliferation and differentiation of corneal epithelium
- Corneal nerve regeneration has been documented in NK with use of autologous serum dosed 6-8 times per day for the first month, tapering to qid

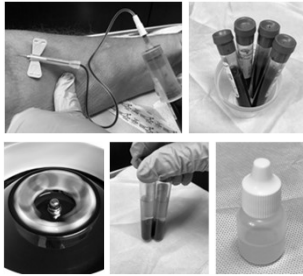
Rao N, Lenzner C, Pflugfelder SC. Corneal nerve regeneration in neurotrophic keratopathy following autologous plasma therapy. *Br J Ophthalmol*. 2010;94(12):1384-89.
 Young A, Li A, Li D, Cheng B, K. Ho, L. Li, Cheng, C, Y. S. Liang, and D. S. C. Lam. "The Use of Autologous Serum Tears in Persistent Corneal Epithelial Defects." *Eye (London, England)* 14, no. 6 (June 2004): 609-14. doi:10.1038/eye4700701.

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Autologous Serum Eye Drops (ASEDs)

Patients own blood

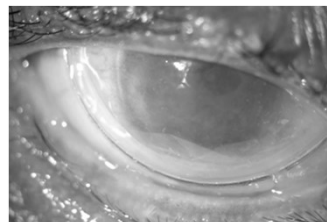
- Blood draw
- Centrifuge
- Separate
- Dilute
 - Commonly 20% to 50%
- Refrigerate between use
 - Good for 1 week
 - Freeze additional supply



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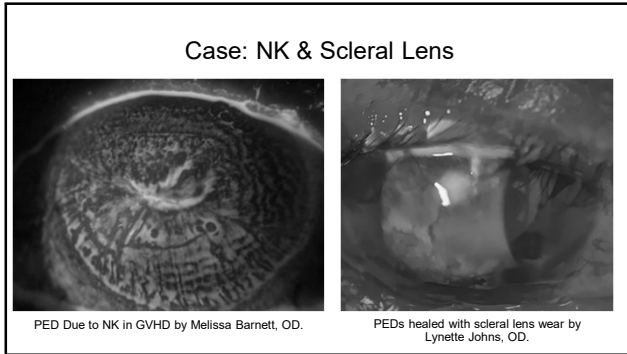
Amniotic Membranes

- Traditionally, transplanted in operating rooms
- Sutureless amniotic membranes
 - Cryopreserved
 - dehydrated
- 75% of patients with NK achieved re-epithelialization in 16 days
- Average time of re-epithelialization of 21 days



Chen HJ, Pires ET, Teng SC. Amniotic membrane transplantation for severe neurotrophic corneal ulcers. *Br J Ophthalmol*. 2002;86(11):1254-53.
 Abadji S, Mariani T, Cheng P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. *Cornea*. 2005;24(6):654-60.
 Shyu H, et al. Sutureless Amniotic Membrane Transplantation for Severe Neurotrophic Keratitis. *Cornea*. 2008;26(12):1118-1122.


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NK Surgical Treatments

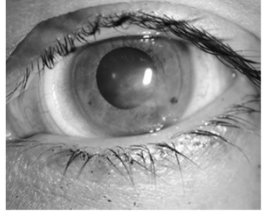
- Additional procedures to supplement care
 - Targeted ocular surface isolating
- Temporary partial or full tarsorrhaphy
 - ie, Lateral tarsorrhaphy
 - ± BCL
 - ± AMT (ie, multilayer or suture fixation)
- Conjunctival flap
- Induced ptosis
 - Neurotoxin
 - Gold weight implant
 - Will impact scleral lens fit
- Temporary punctal occlusion



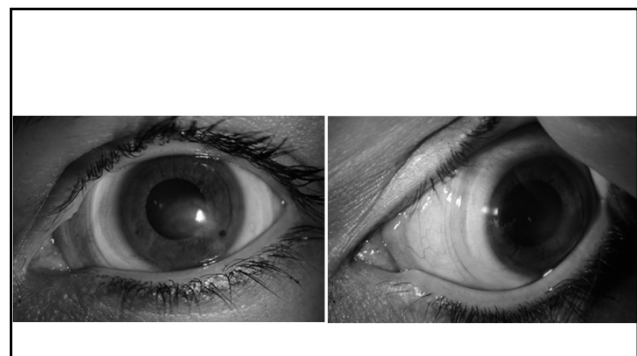
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NK Surgical Treatments

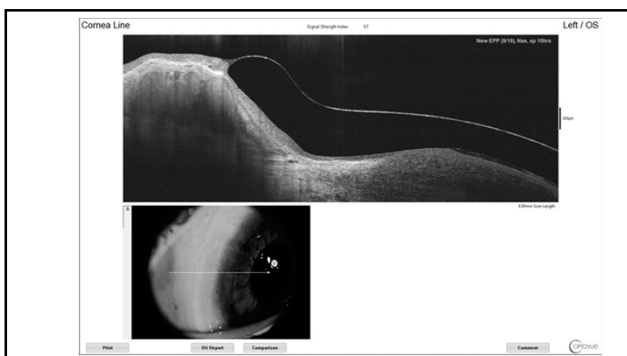
- Corneal neurotization
 - 1st described in 2009 by Terzis et al – to route part of supraorbital or supratrochlear nerve from unaffected eye
 - Effective in restoring sensitivity, but invasive with potential for donor site morbidity
 - Can use sural nerve graft as donor source
 - Minimally invasive techniques developed
 - De-cellularized cadaveric nerve graft attached to smaller piece of healthy donor graft
 - Endoscopic approach



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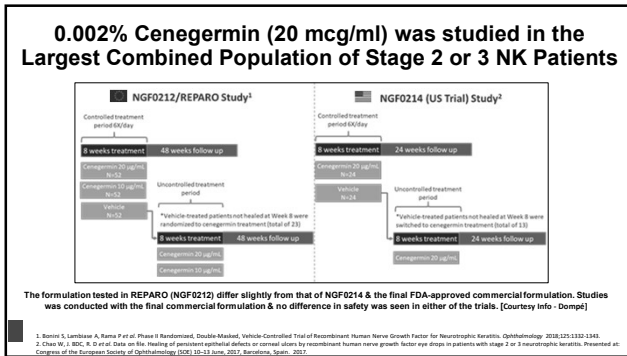
A Novel rhNGF Mimicking Endogenous NGF

- In Aug 2018, FDA approved 0.002% Cenergermin Ophth Soln (20 mcg/mL) with API (Cenergermin-bkbj), which is structurally identical to human NGF protein found in ocular tissues
- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons¹

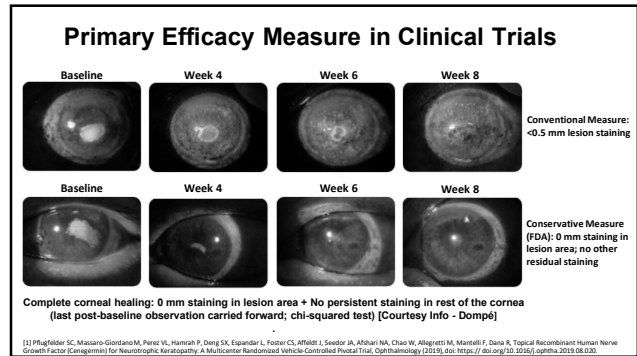


1. Lambaev A, Neme P, Somri S, Caporoglio D, Alse L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med* 2008;358:1174-80. 2. Youlter R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. *JAMA*. 2018;320(13):1309.
 3. Youlter R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. *JAMA*. 2018;320(13):1309

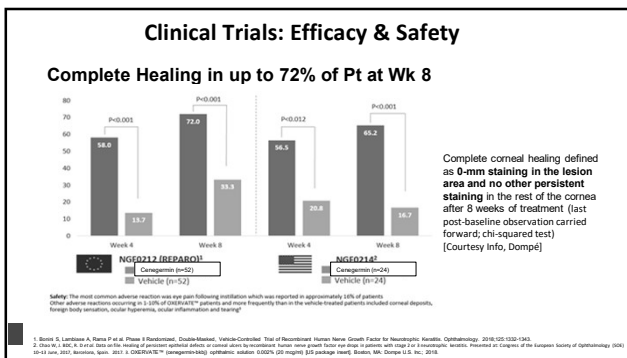
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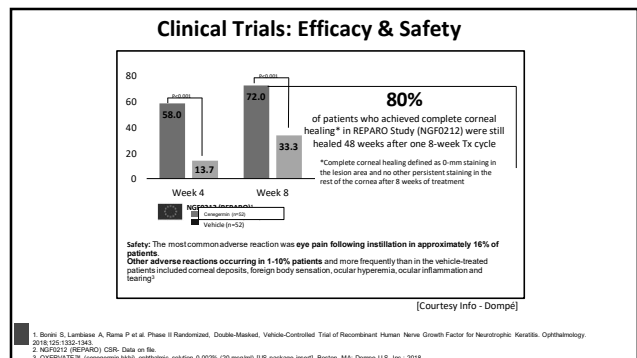
48



49



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51

Clinical Case

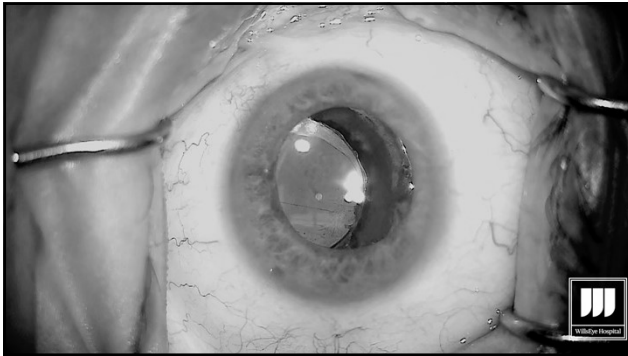
56

63 year old man presented with reduced vision and dislocated IOL in the bag

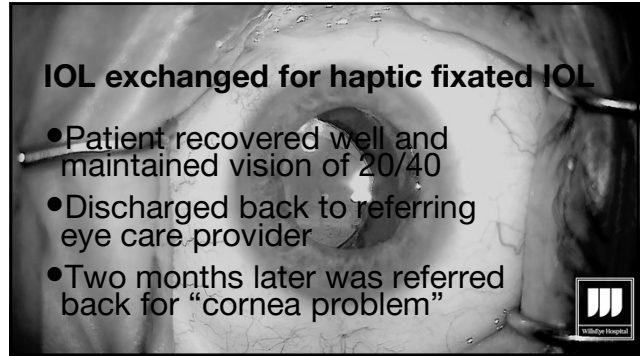
Past Ocular History:

- Treated for 15 years of diabetic retinopathy
- 10 years ago had cataract surgery with IOL (uncomplicated)
- 5 years ago had retinal detachment requiring PPV

57



58



IOL exchanged for haptic fixated IOL

- Patient recovered well and maintained vision of 20/40
- Discharged back to referring eye care provider
- Two months later was referred back for “cornea problem”

59

Initially after surgery vision was good, but now had dropped and he was told he may have an infection

V _{SC}	<	20/30
		20/50
EOM	<	Full
		Full
CVF	<	Full CF
		Full CF
Sens	<	Normal
		Reduced

60

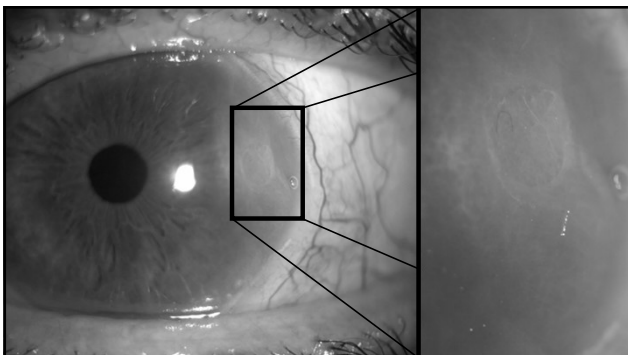
Initially after surgery vision was good, recently had worsened. He was told he may have an infection.

He had tried multiple antibiotics over several weeks

Bandage contact lenses were tried with no success

Self-retaining amniotic membrane was unsuccessful

61



62

**?
Now what**

Diagnosis: Stage II Neurotrophic Corneal Ulcer

Cultures performed

Antibiotics continued

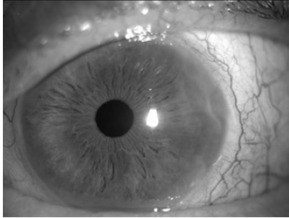
Plug placed in lower puncture

Started recombinant human nerve growth factor Q2H

63

Once starting hNGF symptoms began to resolve relatively quickly and by week 4 of treatment

V< 20/30
SC 20/30



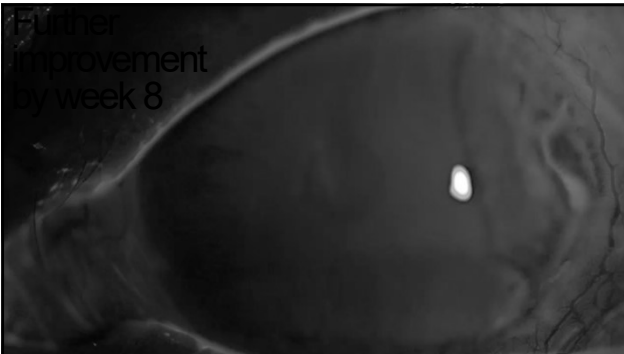
64

Further improvement by week 8



65

Further improvement by week 8



66

Thank you

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Director of Specialty Contact Lenses, Wills Eye Hospital – Cornea Service

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