Neurotrophic Keratitis

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Baylor College of Medicine
Southern Eye Congress 2022

Financial Disclosure

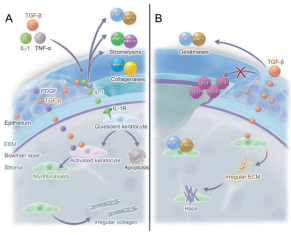
- I have the following financial interests or relationships to disclose:
  - Zeiss
  - Alcon
  - Allergan
  - CorneaGen
  - Novartis
  - Visus
  - Tarsus
  - AcuFocus
  - Dompe

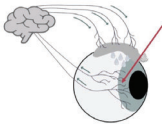
Introduction

- NK is a degenerative corneal disease caused by impairment of trigeminal innervation
- Leads to decreased corneal sensation and subsequent epithelial keratopathies, epithelial defects, stromal ulceration and thinning, and, in severe cases, perforation[a]
- incidence of < 5 per 10,000 people[a,b]
- Underdiagnosed
- Often clinically silent until advanced stages

- a. Dua HS, et al. Prog Retin Eye Res. 2018;66:107-131; b. Sacchetti M, et al. Clin Ophthalmol. 2014;8:571-579.

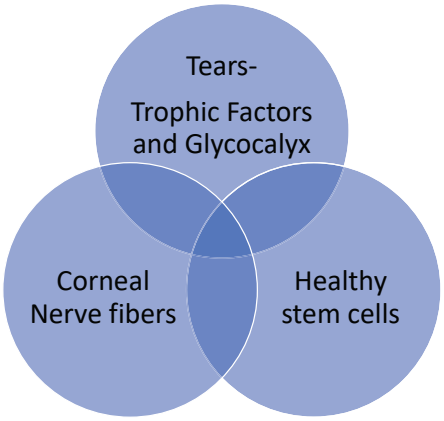
Cornea Homeostasis





CORNEAL NERVE FIBERS

- **Release neuromediators** including acetylcholine, substance P (SP) and calcitonin gene-related peptide (CGRP) that provide trophic support to the ocular surface, **stimulate wound healing, & maintain anatomic integrity**
- When corneal sensory nerves are damaged, there is **impaired corneal physiological renewal/healing**
- May lead to **epithelial breakdown** with a poor tendency to heal



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https://www.nature.com/articles/s41467-019-09331-6: new mechanics effects on cornea differentiation
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010187/: cell migration, cell proliferation, re-stratification, as well as matrix deposition and tissue remodeling. Particularly critical are cell migration and proliferation, which are driven by growth factors released coordinately into the injury sites

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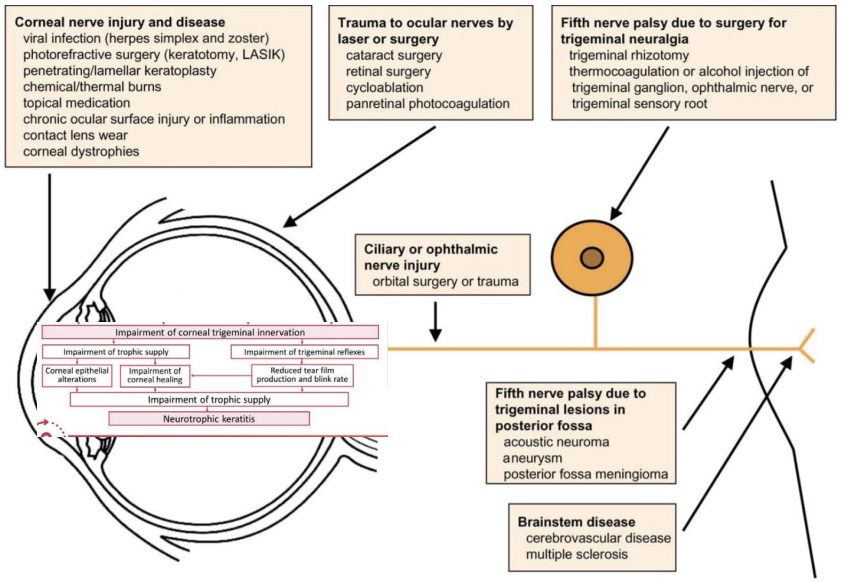

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Fig. 8. A summary of common causes of neurotropic corneal diseases.

Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. Exp Eye Res. 2003 May;76(5):521-42. doi: 10.1016/s0014-4835(03)00050-2. Erratum in: Exp Eye Res. 2003 Aug;77(2):253. PMID: 12697417.
Courtesy of Pflugfelder, MD

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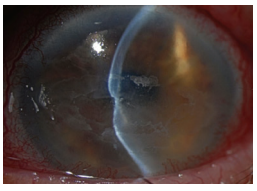
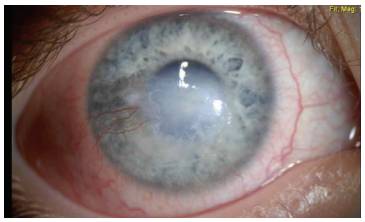
Neurotrophic Keratopathy



- Infectious
  - Herpes zoster, herpes simplex
  - Leprosy
- Toxic
  - Chemical/physical burns
  - Topical anesthetic abuse/chronic use of BAK drops
- Traumatic/Surgical/Iatrogenic
  - 5th nerve palsies (Surgery, Neoplasia, Aneurysm, Facial trauma, strokes)
  - CL use, retina lasers, LASIK
- Systemic Disease
  - Vitamin A deficiency
  - Diabetes mellitus
- Corneal Dystrophies



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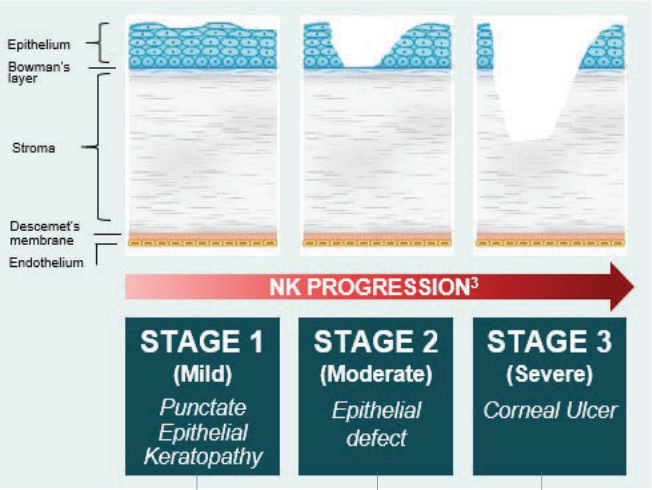
Staging (Mackie Classification)



STAGE 1 (MILD):[1]
Presence of punctate epithelial keratopathy (PEK) and corneal epitheliopathy

STAGE 2 (MODERATE):[2]
Presence of persistent epithelial defect (PED)

STAGE 3 (SEVERE):[2]
Corneal ulcer with stromal involvement

Reduced/ aberrant corneal sensation

Corneal anesthesia

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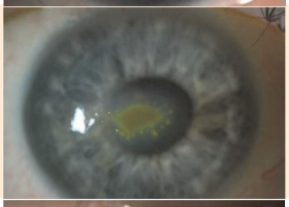
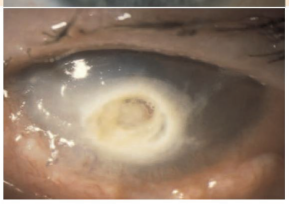
Stage	Clinical photo	Description of signs
1		Decreased TBUT Superficial PEE Gaule spots Irregular epithelium Superficial stromal haze
2		Persistent epithelial defect Descemet's folds AC inflammation
3		Corneal ulceration with stromal loss Stromal thinning with risk of perforation

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Jabbour S, Ashton C, Balal S, Kaye A, Ahmad S. The management of neurotrophic keratitis. Curr Opin Ophthalmol. 2021 Jul 1;32(4):362-368. doi: 10.1097/ICU.0000000000000766. PMID: 33966014.

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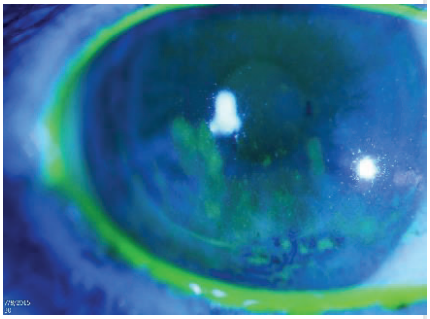
Diagnosis



- Symptoms > clinical signs
- No improvement with traditional methods
- Decreased blink rate
- Corneal aesthesiometer (Cochet-Bonnet) vs. Cotton Tip vs. Dental Floss
  - No drops; unilateral vs. bilateral
- Appearance of epithelium

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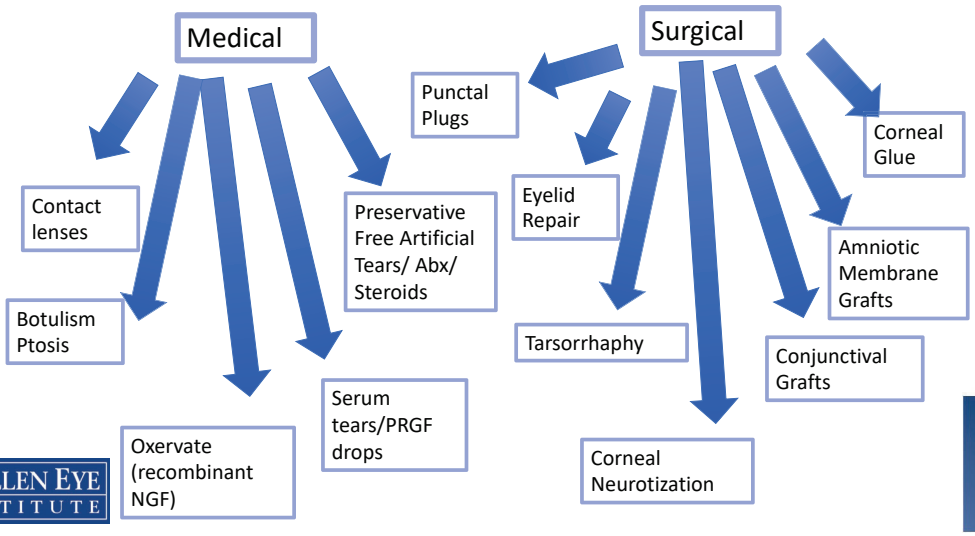
Neurotrophic Keratopathy Treatment



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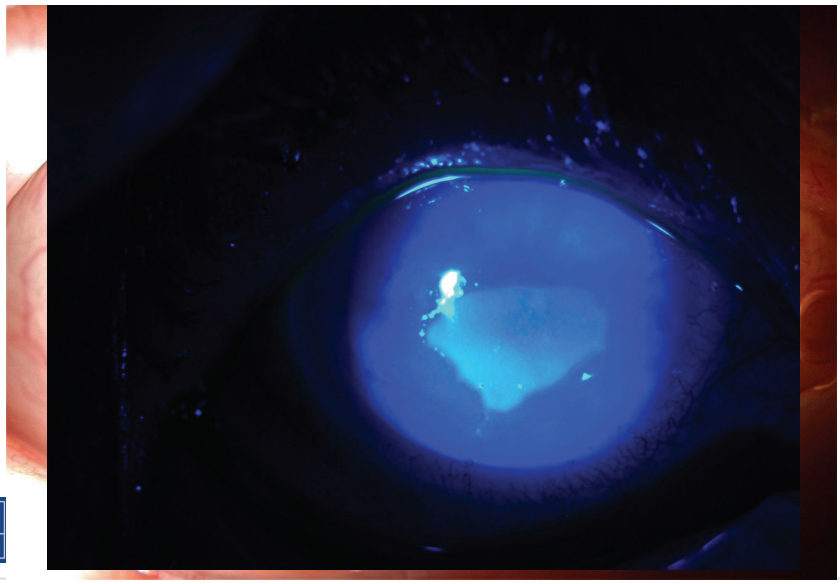
Case Presentation



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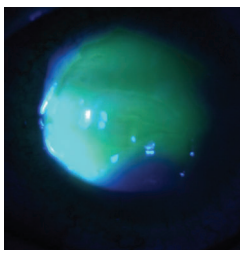
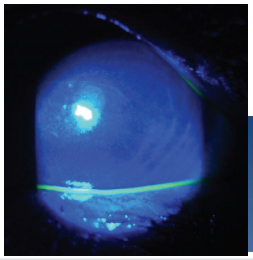
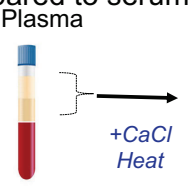
Blood Products

- Contain same biologically active constituents as tears
  - TGF-β, IL 13, Lactoferrin, EGF, Vit A, NGF
- Serum tears are plasma tears devoid of clotting factors like fibrinogen
- Plasma rich blood growth factors (PRGF)
  - Higher concentration of platelet factors & more effective compared to serum tears
  - FDA approved kit







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Photos courtesy of Stephen Pflugfelder, MD

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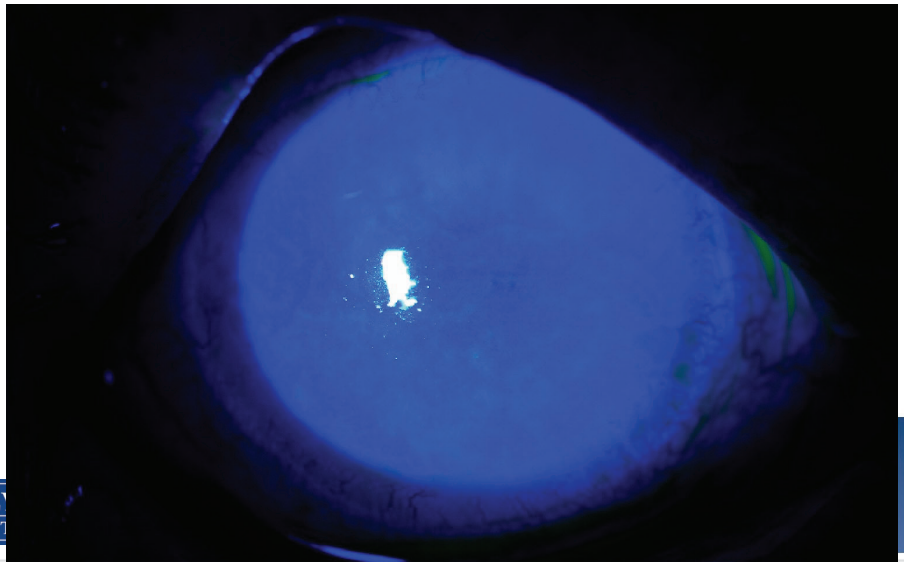
Case Presentation



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Amniotic Membrane

- Has anti-inflammatory, anti-scarring, and anti-angiogenic effects
- Maintains limbal niche cells to support the quiescence of limbal epithelial stem cells toward regeneration

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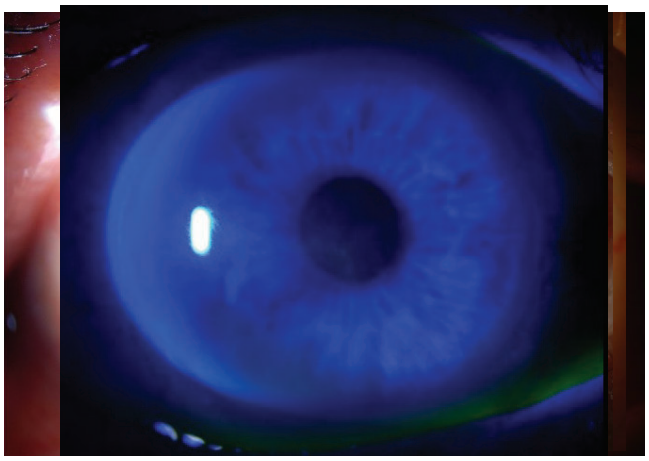
Amniotic Membrane



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Format: Abstract Send to

Cont Lens Anterior Eye. 2019 Feb;42(1):117-122. doi: 10.1016/j.clae.2018.09.004. Epub 2018 Sep 25.

Case series: Extended wear of rigid gas permeable scleral contact lenses for the treatment of persistent corneal epithelial defects.

Khan M[1], Manuel K[1], Vegas B[1], Yadav S[1], Hemmati R[1], Al-Mohtaseb Z[2].

Author information

1 Cullen Eye Institute, Department of Ophthalmology, Baylor College of Medicine, Houston, Texas, USA.
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Abstract

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METHODS: Eight eyes of eight patients with persistent corneal epithelial defects were treated with Blanchard Onefit 2.0 Scleral lens, BostonSight Scleral lens, and BostonSight PROSE device and were observed for defect resolution and improvement in best-corrected visual acuity over the duration of treatment.

RESULTS: All eyes observed complete re-epithelialization with a mean time of 11.1 ± 5.5 days. At the conclusion of the treatment, visual acuity improved in all but one patient. No complications were observed during treatment.

CONCLUSIONS: Scleral lenses provide the corneal epithelium with hydration, oxygen permeation, and protection from mechanical forces; thereby facilitating healing of persistent corneal epithelial defects. This case series demonstrates the successful use of continuous wear scleral lenses in a number of patients for the treatment of persistent epithelial defects refractory to other interventions.

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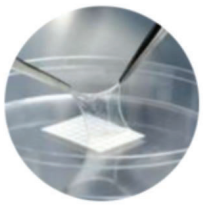
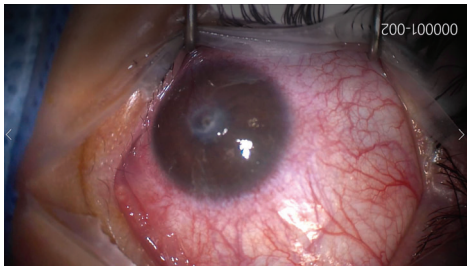
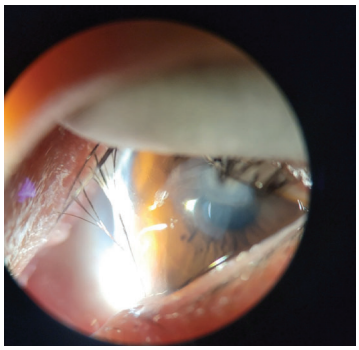
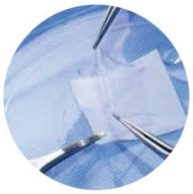
Surgical placement of frozen AMT



- Good option for management of perforations and pending perforations to delay need for keratoplasty.







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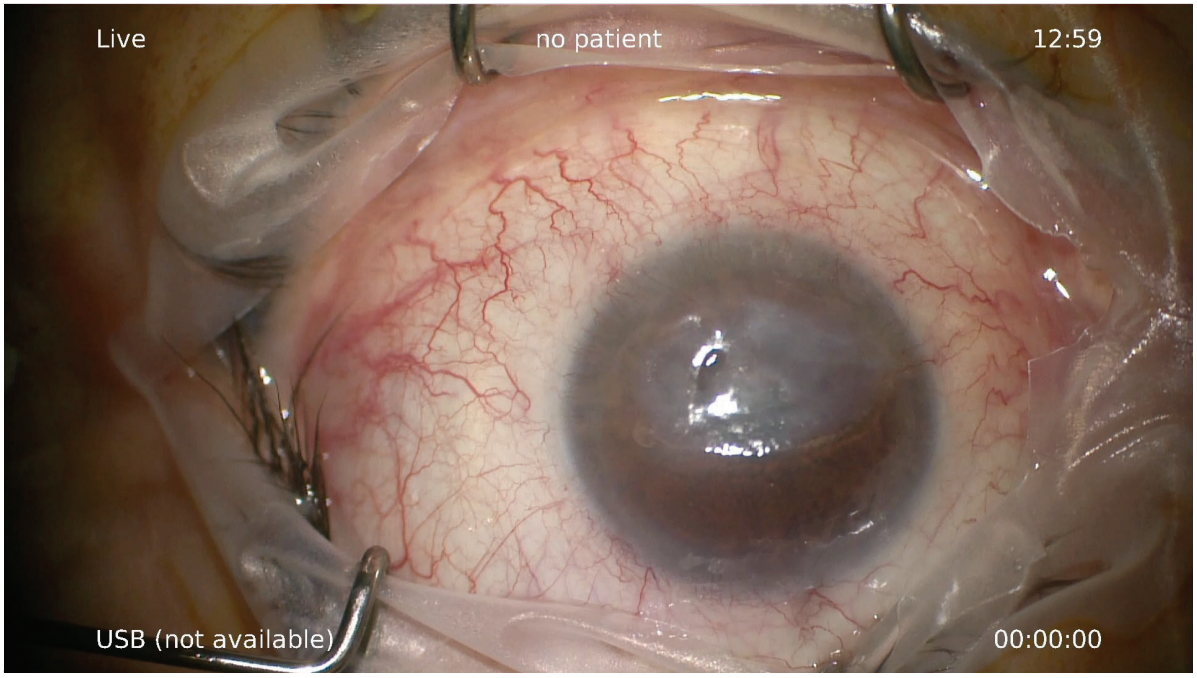
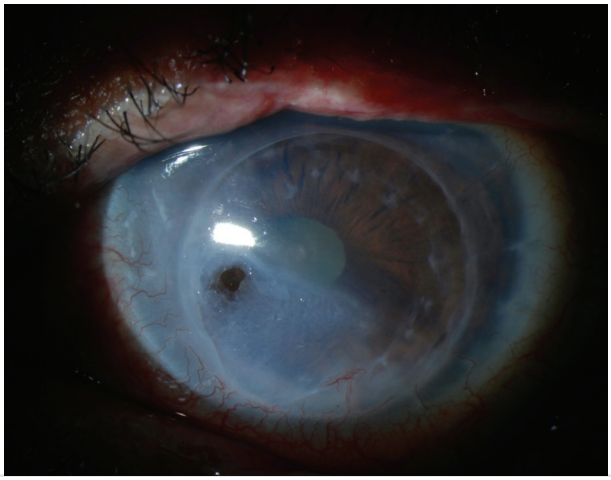


Delay or Avoid Transplantation in Neurotrophic Ulceration



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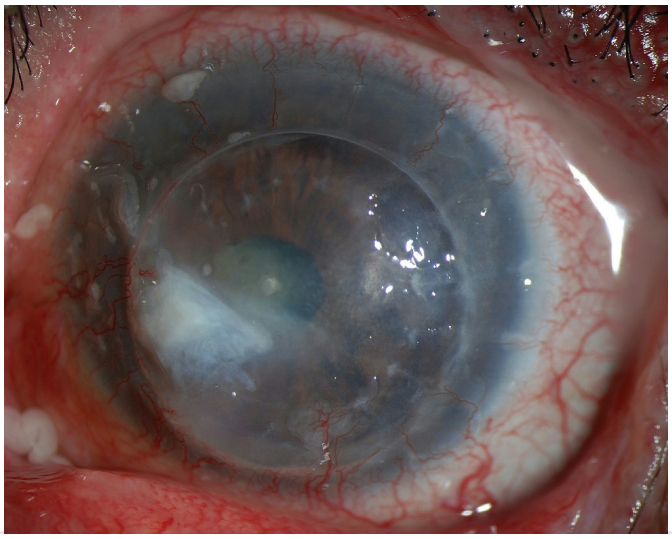
POM#1



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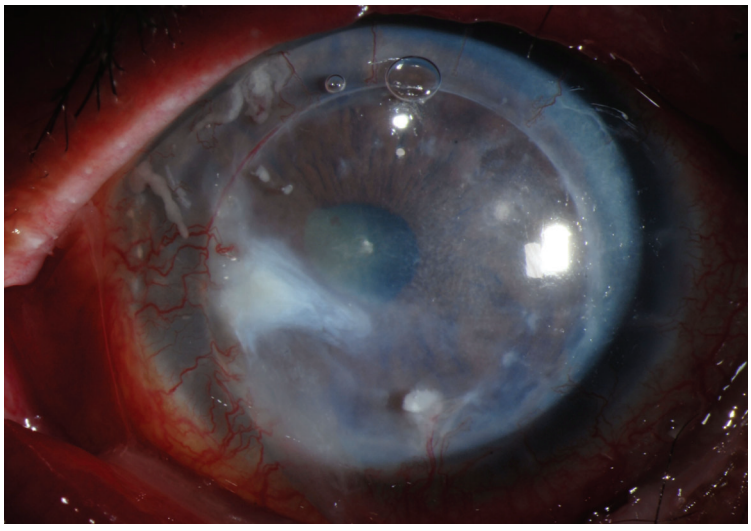
POM#3 s/p PROSE



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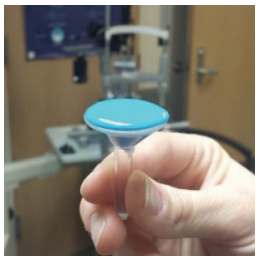
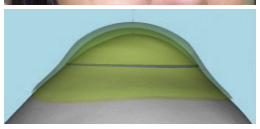
Scleral Lenses Eye Print PRO

- EyePrintPRO™ is a prosthetic scleral cover shell which improves vision by creating a new, smooth, refractive surface for the eye
- Impression is taken with a proprietary polymer that captures the precise curvatures of the entire ocular surface
- 3D scanned and a prosthetic scleral cover shell is designed around the surface irregularities





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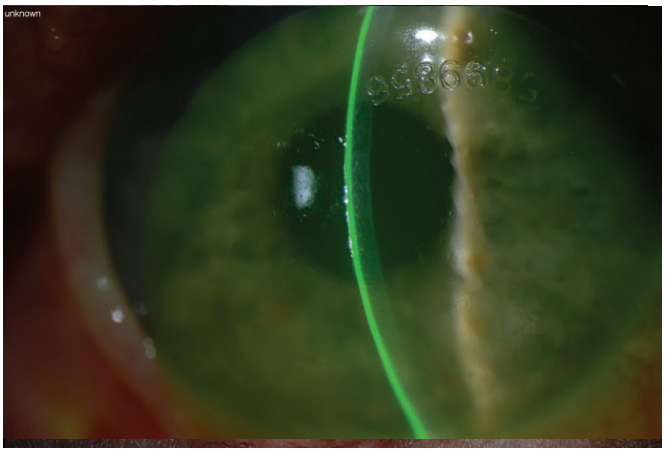
Eye Print PRO



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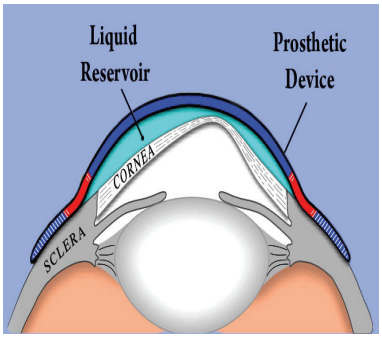
PROSE

- PROSE: “prosthetic replacement of the ocular surface ecosystem”
- Diameter: 17.5-23mm
- Rests on bulbar conjunctiva
- Vaults cornea (no touch)
- Custom designed to treat distorted corneal surface or ocular surface disease



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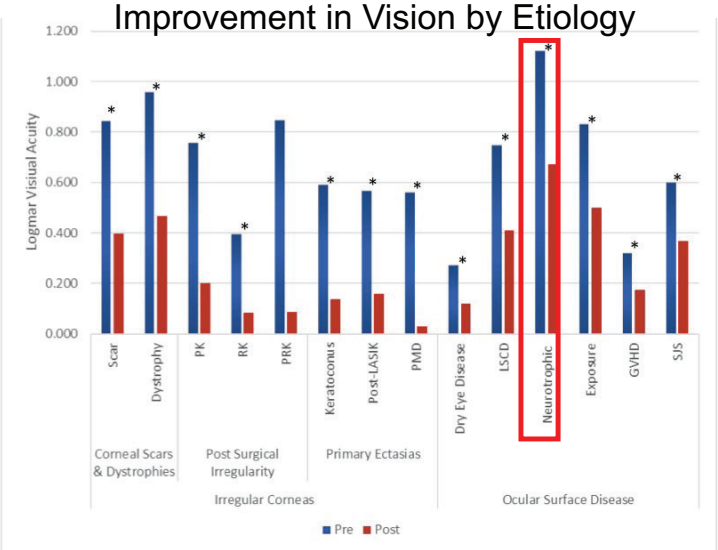
Ocul Surf. 2018 Feb 6. pii: S1542-0124(17)30263-X. doi: 10.1016/j.jtos.2018.01.003. [Epub ahead of print]

Assessment of the Prosthetic Replacement of Ocular Surface Ecosystem (PROSE) scleral lens on visual acuity for corneal irregularity and ocular surface disease.

Parra A[1], Roth BM[1], Nguyen TM[1], Wang L[1], Pflugfelder SC[1], Al-Mohtaseb Z[2].

Improvement in Vision by Etiology



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Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy

A Multicenter Randomized Vehicle-Controlled Pivotal Trial

Stephen C. Pflugfelder, MD,[1] Mina Massaro-Giordano, MD,[2] Victor L. Perez, MD,[3] Pedram Hamrah, MD,[4] Sophie X. Deng, MD, PhD,[5] Ladan Espandar, MD, MS,[6,7] C. Stephen Foster, MD,[8,9] John Affeldt, MD,[10] John A. Seedor, MD,[11] Natalie A. Afshari, MD,[12] Wendy Chao, PhD,[13] Marcello Allegretti, PhD,[13] Flavio Mantelli, MD, PhD,[13] Reza Dana, MD, MPH[9,14]

Cenegermin (Oxervate)

- Recombinant human NGF (rhNGF) produced in Escherichia coli
- Developed based on studies with murine nerve growth factor (NGF)
- NGF0212/REPARO and NGF0214 trials demonstrated efficacy and safety
- NGF0214 showed statistically significant healing compared to control

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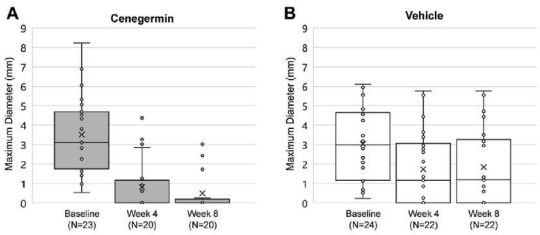

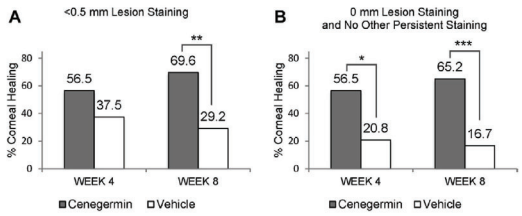

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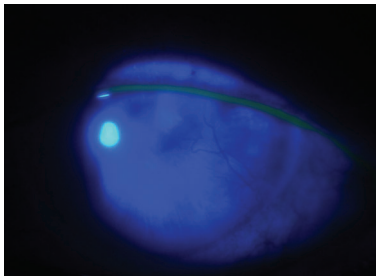
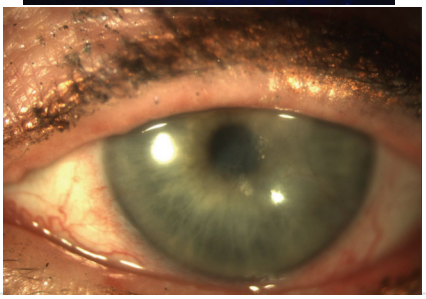
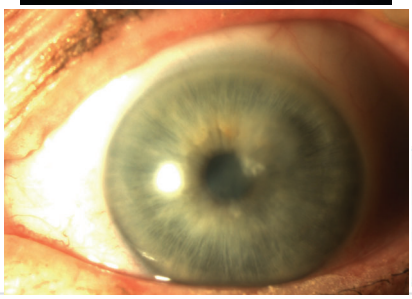
Pre Oxervate

Post Oxervate

Photo courtesy of Stephen Pflugfelder, MD







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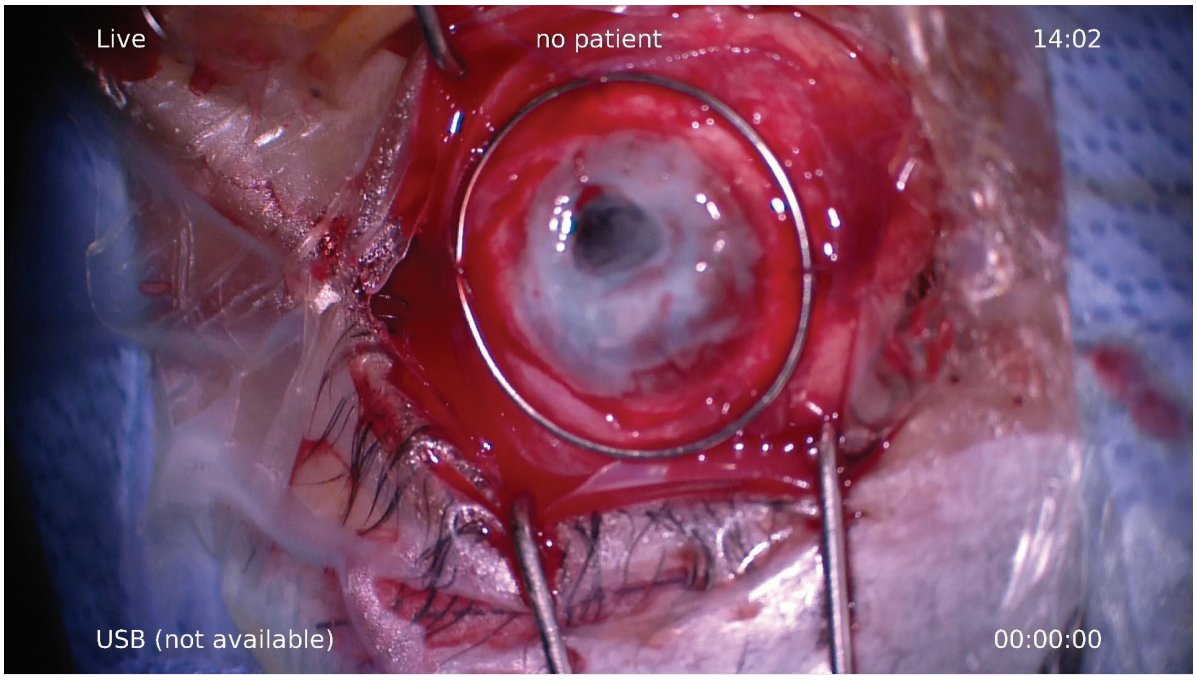
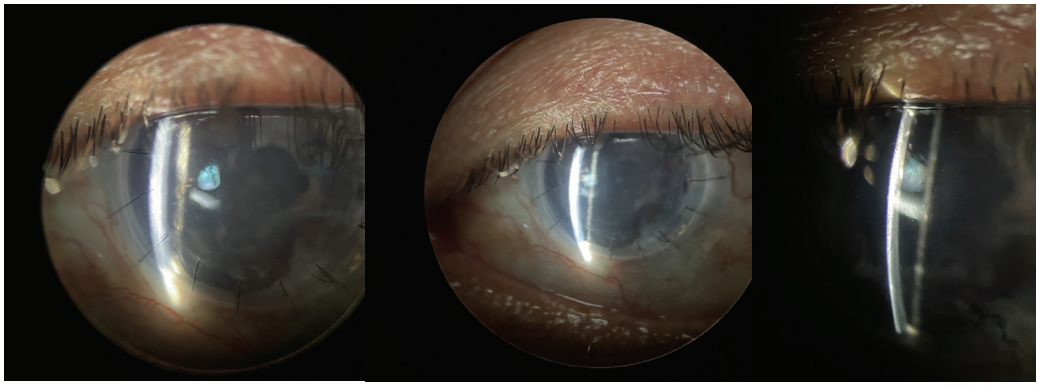


POM # 6 and post Oxervate



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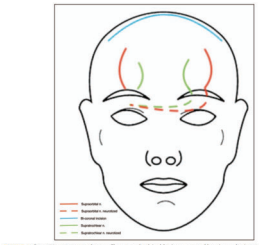
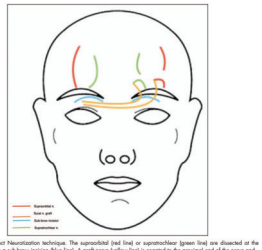
Corneal Neurotization

- Donor nerve graft is co-apted to the damaged nerve
- Transfer of a healthy nerve segment to the corneo-limbal area, reestablishing a basis for sub-basal plexus regeneration
- Corneal reinnervation can be performed by direct nerve transfers or by nerve graft interpositions





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Corneal Neurotization

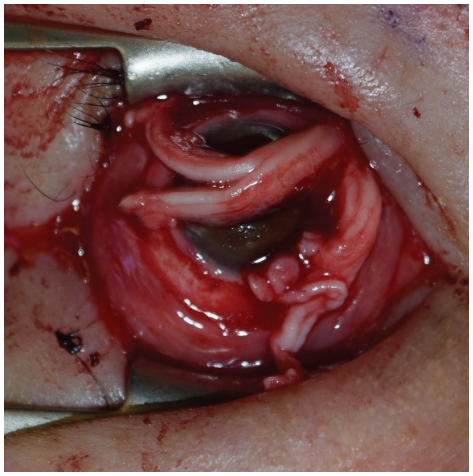

Photo courtesy of Richard Allen, MD

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Outcomes of corneal neurotization

- Most studies have reported a **subjective improvement at 6 months**
- Corneal **esthesiometry may lag behind**
  - Cochet–Bonnet esthesiometry was the method of choice in older children and adults
  - In children less than 2 years of age, esthesiometry was replaced with surrogate measures of corneal sensation notably corneal vascularization, ocular surface healing and decreased fluorescein uptake
- Studies note a period of **ocular pain and discomfort** after the procedure that is attributed to the **subjective sensory recovery** of the neurotized cornea. This usually **precedes the epithelial healing process**
- Evidence also suggests that only the **corneal nerves regenerate without the normal reflex mechanisms** involved with the trigeminal nerves. Catapano et al. reported absence of the blink reflex and minimal effect on lacrimal gland secretion even after full neurotization occurs

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Conclusions

- Many options for in office medical and surgical therapies for neurotrophic/exposure keratitis
- Medical options include serum tears/PRGF drops and therapeutic contact lenses
- Surgical options include amniotic membranes and tarsorrhaphies
- A combination of therapies is needed at times

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Thank you!

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