‘Stain Without Pain’

Current management of Neurotrophic Keratitis

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- I do not have any potential conflict of interest

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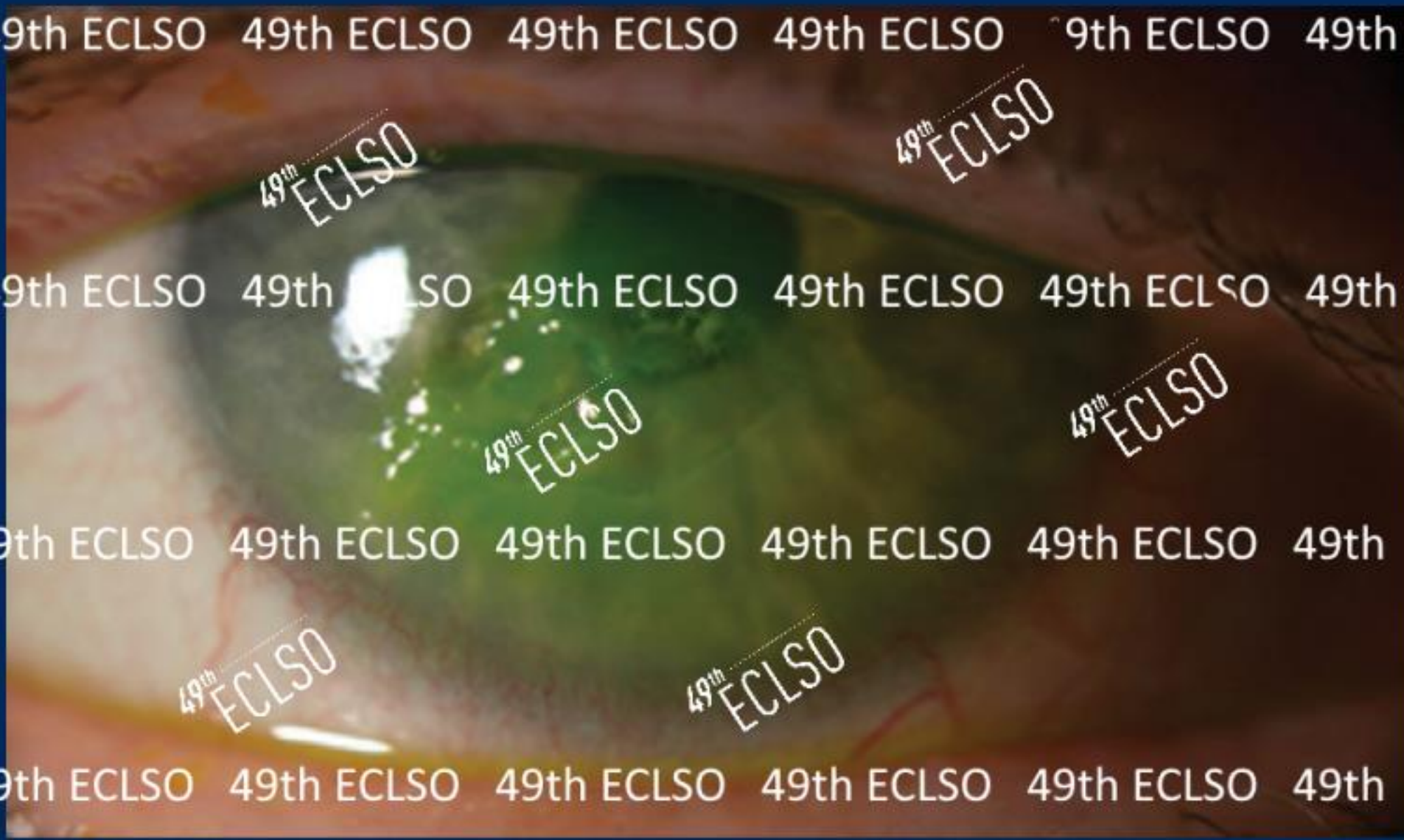

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Neurotrophic Keratitis

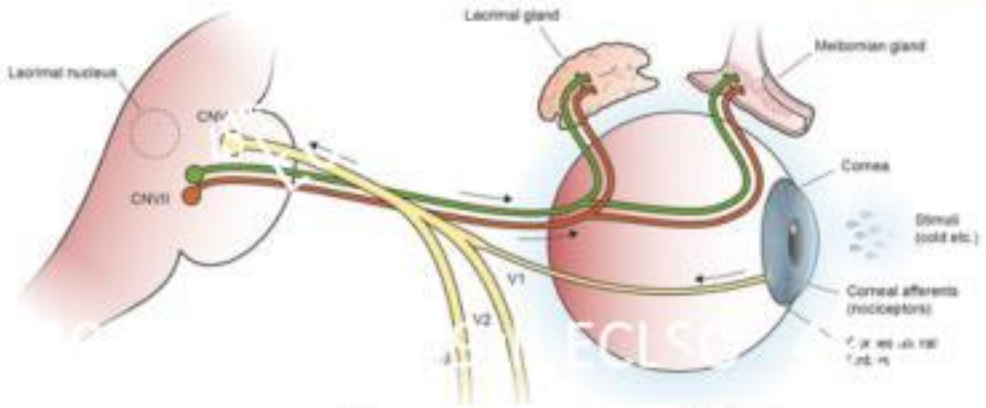
- A progressive degenerative disease of the cornea caused by impairment of nerves responsible for sensory innervation.
- *results in spontaneous corneal epithelial breakdown, compromised healing, and corneal ulceration, melting, and perforation.*
- The hallmark of neurotrophic keratitis is reduced or absent corneal sensation.

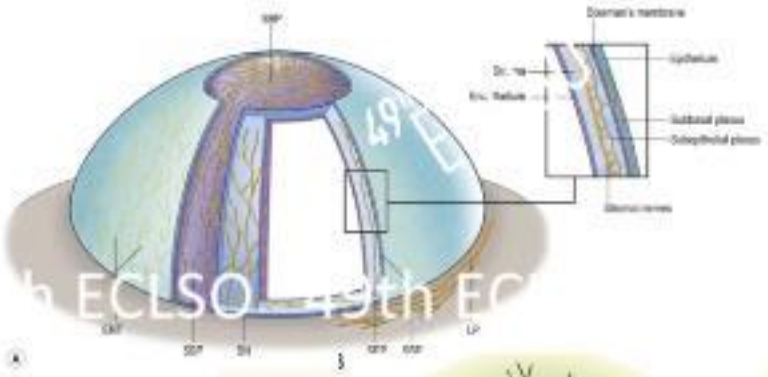
Neurotrophic Keratitis (ORPHA137596)

- Neurotrophic keratitis is classified as a rare disease and estimated to affect fewer than 65.000 people in the US
- Estimated prevalence is less than 5 in 10.000
  - 12.3 % of HZO keratitis
  - 6 % of HSV keratitis
  - 2.8 % after surgical procedures for trigeminal neuralgia

Corneal nerves

- V1 (ophthalmic N)
  - Nasociliary N➔ Long ciliary nerves
- Sensation to mechanical, thermal, chemical stimuli
- Elicit two reflex arcs via sensory feedback
  - motor arc➔ blinking
  - Autonomous arc ➔ tear secretion
- Provide trophic support & maintain surface homeostasis
  - denervation causes decreased mitosis, intracellular edema, loss of microvilli, abnormal basal lamina



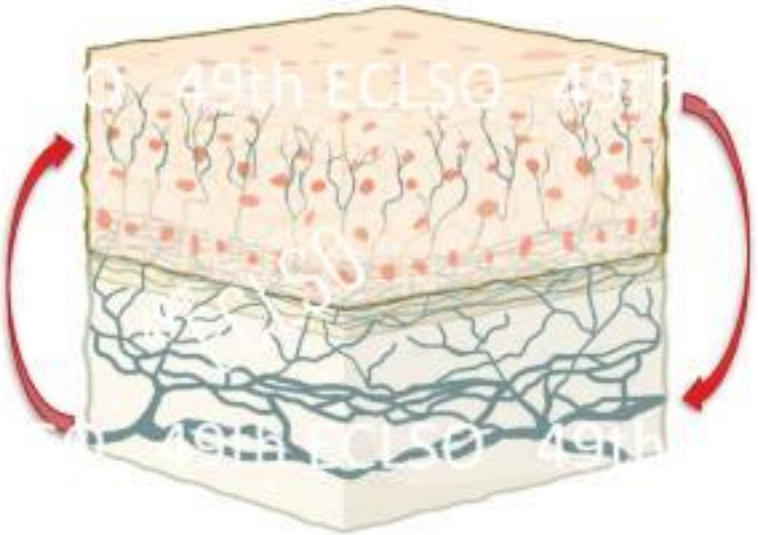


Corneal nerve fibers and corneal epithelium mutually support each other

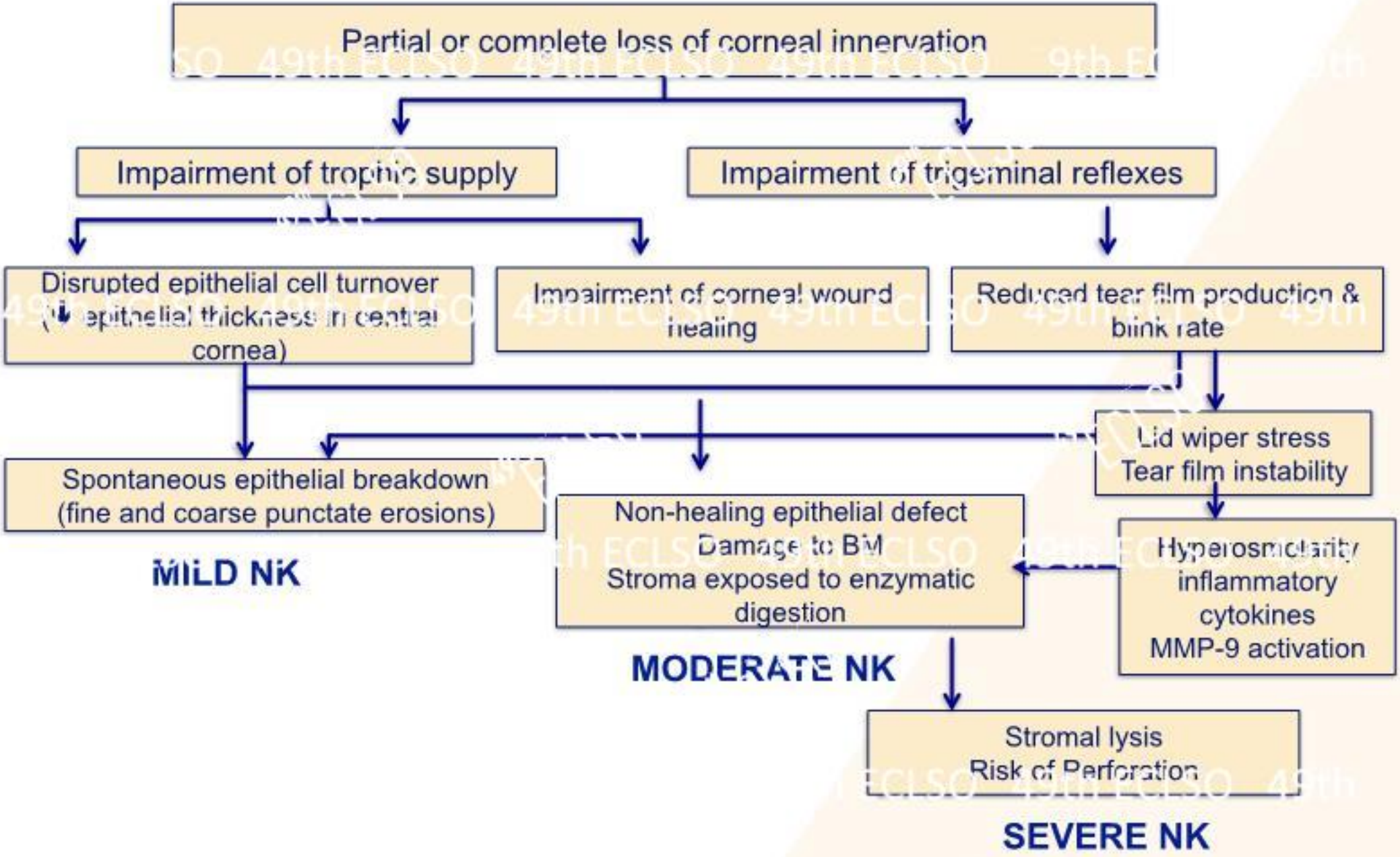
Sensory-
- Substance P
- CGRP
- Neurokinin A
- PACAP
- Galanin

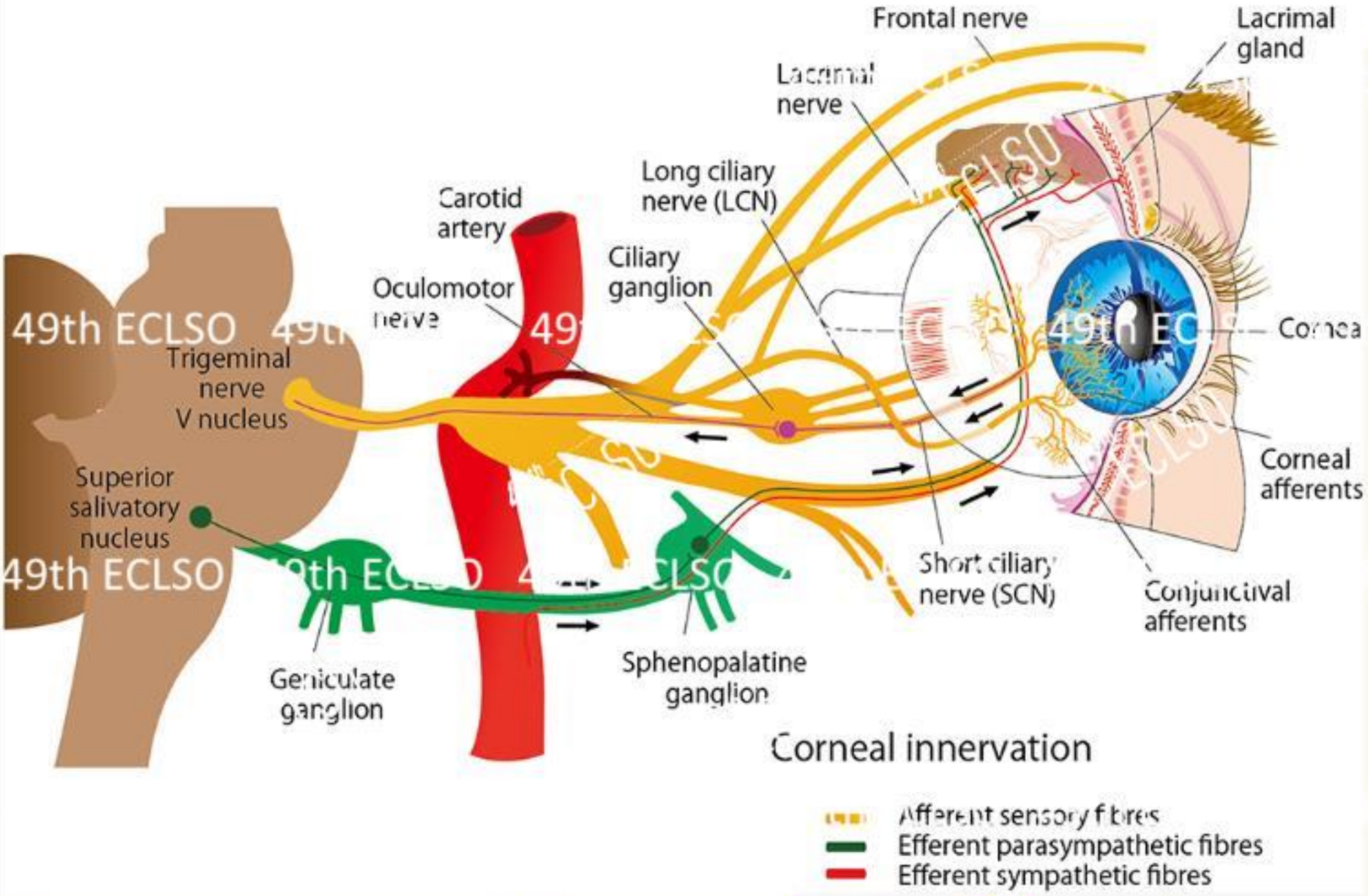
Sympathetic-
- NE
- NPY
- Serotonin

Parasympathetic-
- VIP
- Met-enkephalin
- Acetylcholine



Nerve growth factor (NGF)
Neurotrophin-3 (NT-3)
Neurotrophin-4 (NT-4)
Ciliary neurotrophic factor (CNTF)
Glial cell derived neurotrophic Factor (GDNF)


Partial or complete loss of corneal innervation
Impairment of trophic supply
Impairment of trigeminal reflexes
Disrupted epithelial cell turnover
(↓ epithelial thickness in central cornea)
Impairment of corneal wound healing
Reduced tear film production & blink rate
Lid wiper stress
Tear film instability
Spontaneous epithelial breakdown
(fine and coarse punctate erosions)
MILD NK
Non-healing epithelial defect
Damage to BM
Stroma exposed to enzymatic digestion
MODERATE NK
Hyperosmolarity
inflammatory cytokines
MMP-9 activation
Stromal lysis
Risk of Perforation
SEVERE NK



Dua H et al. Prog Ret Eye Res 2018; 66: 107-131

NK ETIOLOGIES

OCULAR	SYSTEMIC	CNS	GENETIC
HSV, HZO	Diabetes	Stroke	Riley-Day Syn
Corneal sx (LASIK, PRK, PKP/DALK)	Multiple sclerosis	Aneurysms	Goldenhar-Gerlin Syn
Retinal sx (PPV, PRP, scleral buckle)	Amyloidosis	Neoplasms	Mobius Syn
Chemical Trauma	Vit A deficiency	Neurosurgical procedures	Familial corneal hypoesthesia
Drug toxicity (BAK, glaucoma meds, NSAIDs, anesthetics)		Procedures for trigeminal neuralgia	
Contact lens wear			
Eye rubbing			
Chronic inflammatory OSD (dry eye, SJS, GVHD)			
Lagophthalmos			

Symptoms

- Little/no pain and discomfort
- Dryness
- Fluctuating vision
- Trouble reading for prolonged period of time
- Photophobia
- Redness

Diagnosis of NK

1

CLINICAL HISTORY

- HSV/HZO
- DM
- Contact lens use
- Chemical trauma
- Ocular surgery
- Topical medications

2

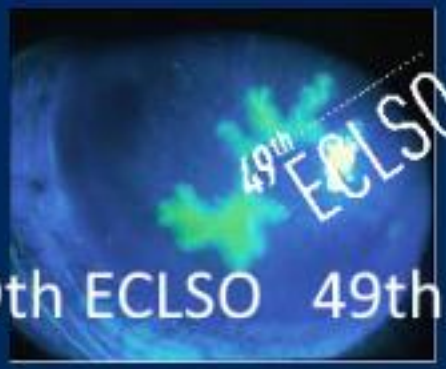
CORNEAL SENSITIVITY TESTING

Cotton wisp

Dental floss

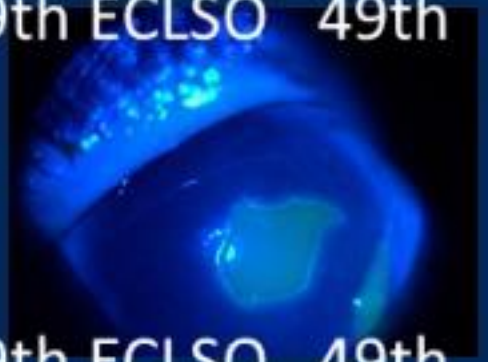
3

SLIT-LAMP EXAM



Cochet-Bonnet esthesiometer

- Present
- Decreased
- absent



Mackie Stage 1

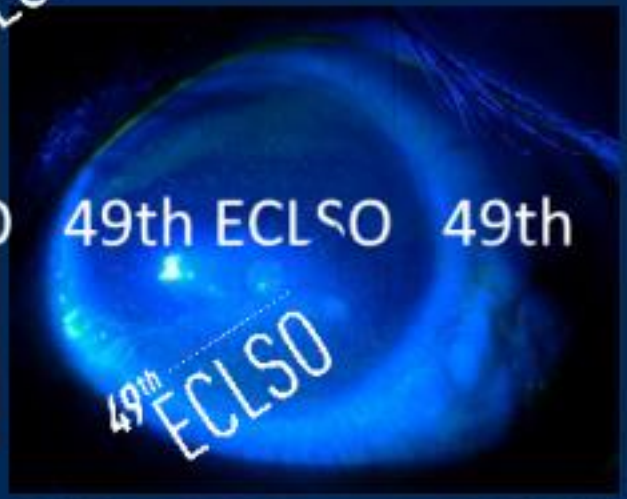
Symptoms:

dry eye like symptoms

Fluctuating vision

Signs

- Dull, cloudy appearance
- Epithelial irregularity
- Punctate epithelial staining
- Inferior conjunctival staining
- Decreased TBUT
- Superficial NV scarring



Dua H et al. Prog Ret Eye Res 2018; 66: 107-131

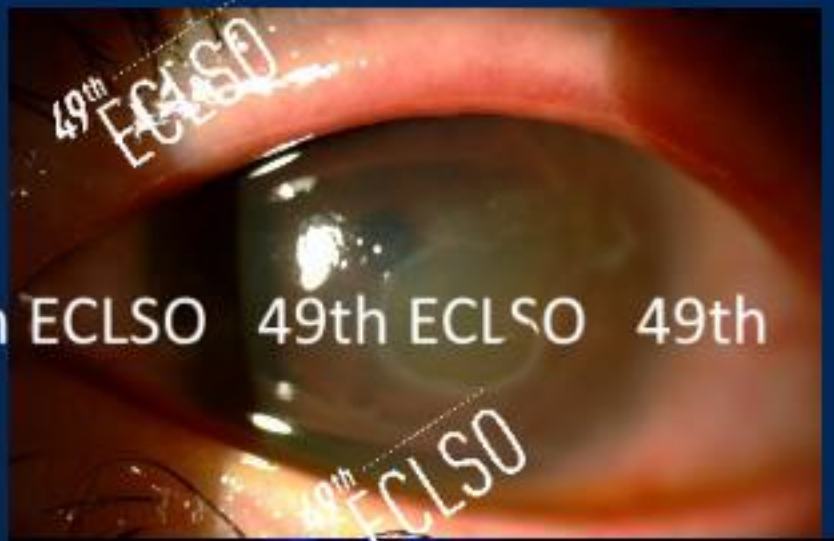
Mackie Stage 2

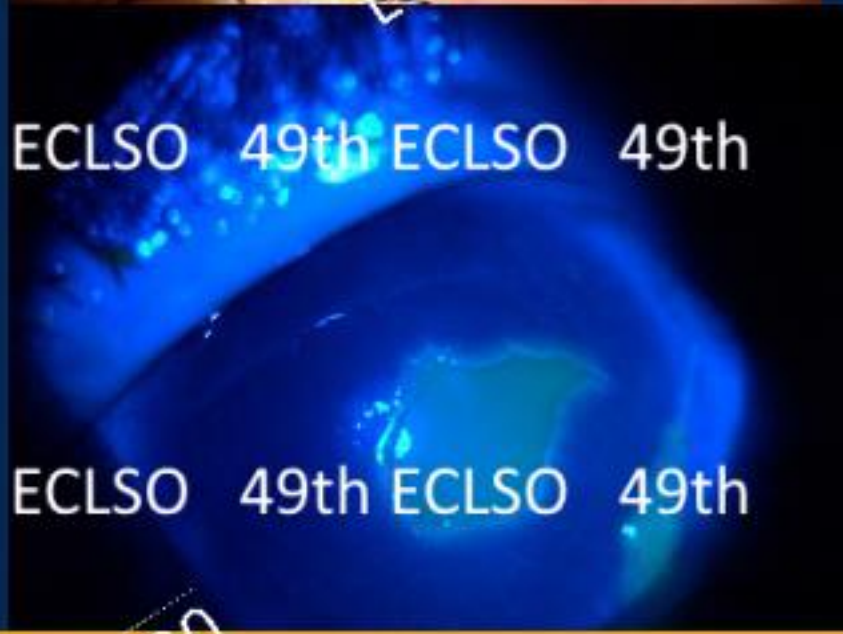
Symptoms

- + Blurred vision

Signs

- PED with smooth & rolled edges
- D-folds & stromal swelling
- Stain without pain
- May be associated with AC inflammation





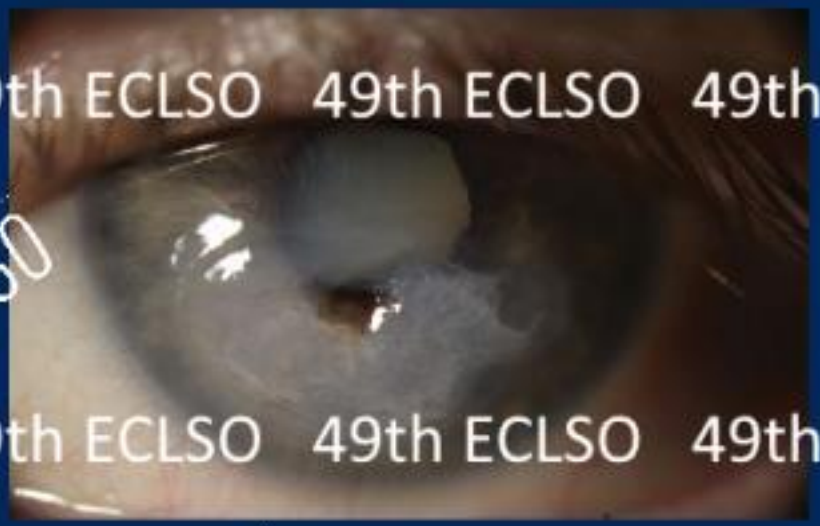
Mackie Stage 3

Symptoms

- +++ visual disruption

Signs

- Corneal ulcer with stromal involvement
- Stromal melting
- Superinfection
- Perforation



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Treatment Options for NK

Therapy
Preservative-free artificial tears
Anti-inflammatory tx
Punctal plugs
Bandage contact lenses
+/-Serum/umbilical cord/PRP
rhNGF

Therapy
+ topical antibiotics
rhNGF
MMP inhibitors
Scleral lenses (+/- serum tears)
Amniotic membrane (sutured/ self-retained)
Tarsorrhaphy

Therapy
+
rhNGF
Tarsorrhaphy
Glue
Conjunctival flap
Corneal grafts
Corneal neurotization

Disease Severity

Stage 1 **Stage 2** **Stage 3**

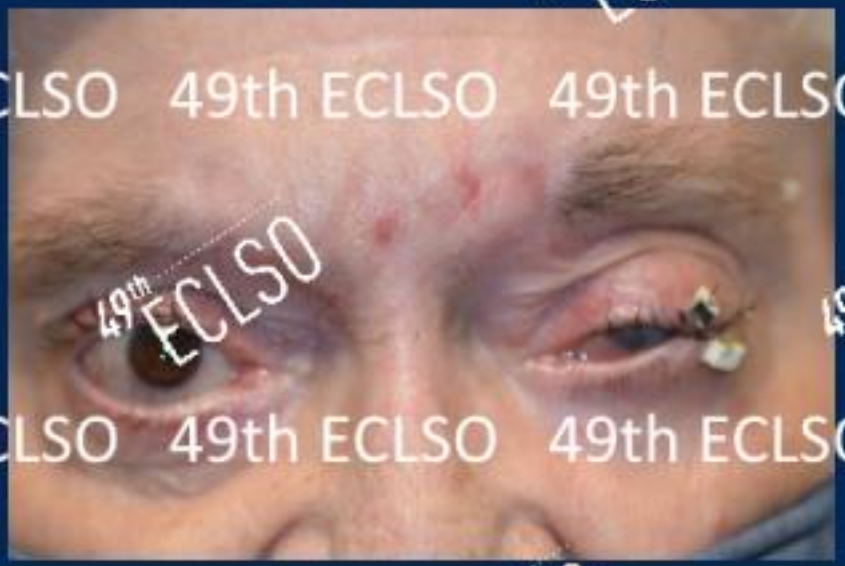
Stage 1 NK

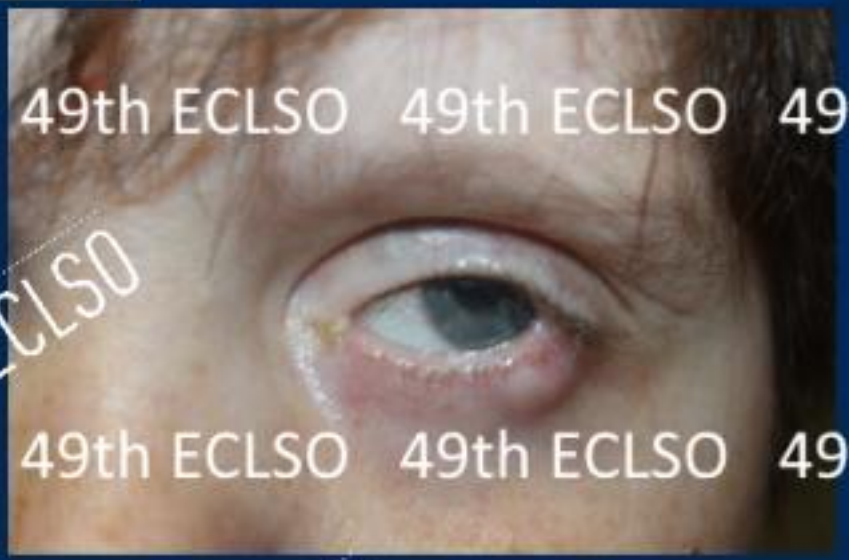
- Discontinue all topical meds that can be toxic to OS
- Preservative-free artificial tears
- Anti-inflammatory therapy (avoid NSAIDs)
- Punctal occlusion
- Correct lid abnormalities
- Bandage soft lenses
- +/- blood products/ biologic extracts drops
- +/- rhNGF

Stage 2 NK

- Debridement of loose edges
- Prophylactic topical antibiotics (moxifloxacin)
- Prevention of melting
  - N-acetyl cysteine, systemic doxycyline, medroxyprogesterone, vit-C
- Eyelid closure (tape/ temporary tarsorrhaphy)
- Bandage lenses or scleral lenses
- Serum/plasma drops
- rhNGF
- Amniotic membrane
- RGTA drops
- Insulin drops
- Corneal neurotization

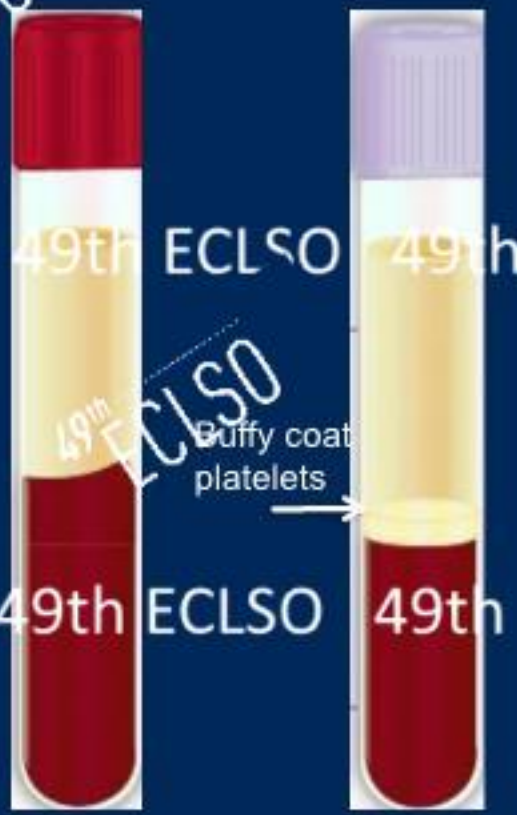
Tarsorrhaphy





Blood derived products

- Serum eye drops
  - Autologous/Allogenic (20%, 50%)
- Plasma Eye drops
  - platelet rich plasma (PRP)
  - Platelet rich plasma in Growth factors (PRGF)
    - Higher conc of PDGF, EGF, VGF, angiopoietin-1
- Umbilical cord serum/platelet lysates (20%)
  - Less inflammatory factors than peripheral blood
  - Higher conc of EGF, NGF, TGF-β than peripheral blood
  - Unique molecules with immune suppressive properties (NKG2D- MIC & ULBP1)



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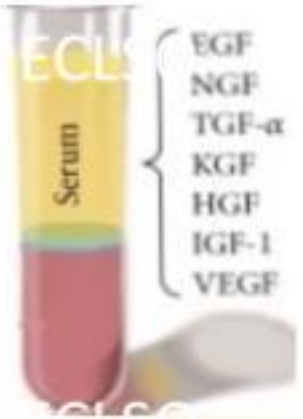
Serum Eye drops

	TEARS	SERUM
Ph	7.4	7.4
Osmolality	308	290
Albumin (mg/l)	54	35-55
EGF (ng/ml)	1.5	0.7
TGF-b (ng/ml)	2-10	6-33
Vitamin A (mg/ml)	0.02	46
Lysozyme (mg/ml)	1.4	6
IgA (ug/ml)	150	2
Fibronectin (ug/ml)	21	205
Hepatocyte GF, NGF, IGF-1, Substance P, Complement, Fibroblast GF, cCRP, other Ig, etc.		✓

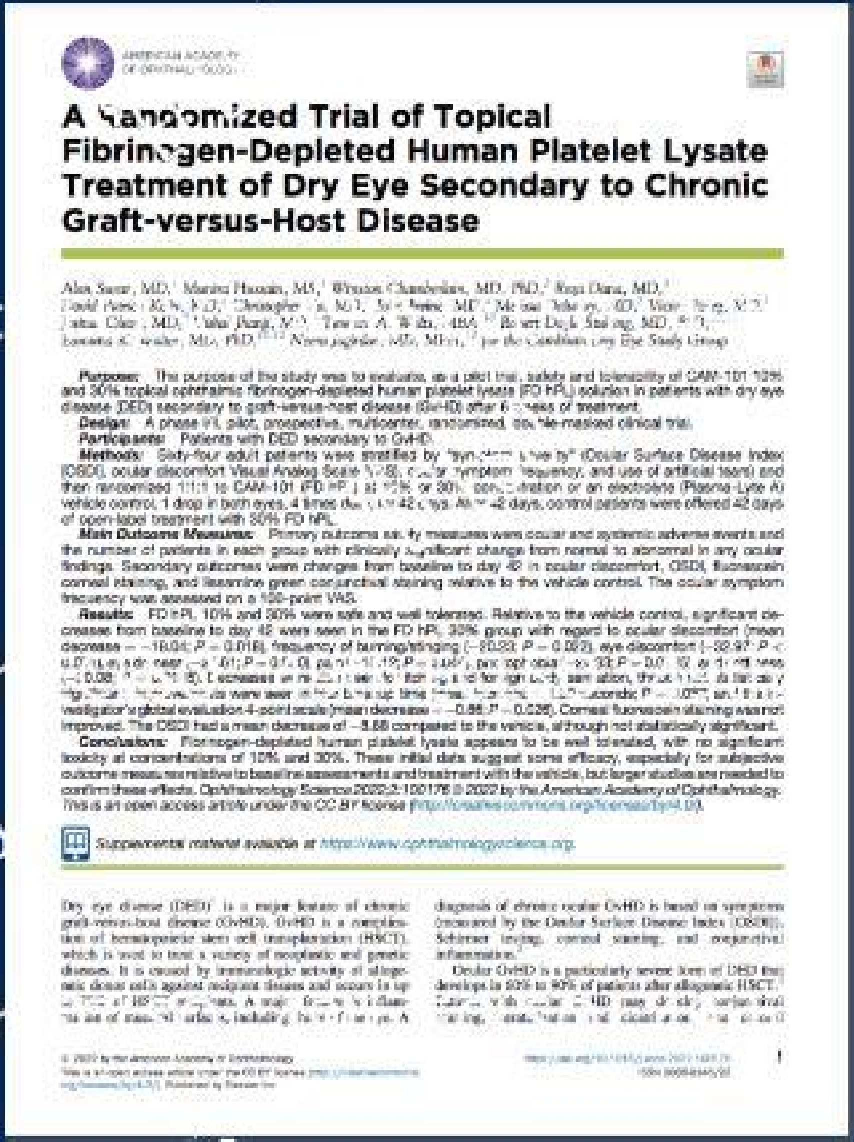


10%, 15%, 20%, 30% and 40%

Vital Tears

Fibrinogen depleted Platelet lysate drops
Elate Ocular ® (Cambium Medical Technologies)

- Cell-free biologic product
- Prepared from pooled platelet lysates
- Fibrinogen is depleted
- 30% dilution
- Promising results from Phase I/II in GVHD
- Phase III trial is ongoing


A Randomized Trial of Topical Fibrinogen-Depleted Human Platelet Lysate Treatment of Dry Eye Secondary to Chronic Graft-versus-Host Disease

Design: A phase I/II, pilot, prospective, multicenter, randomized, double-masked clinical trial.

Participants: Patients with DED secondary to GvHD.

Conclusions: Fibrinogen-depleted human platelet lysate appears to be well tolerated, with no significant toxicity at concentrations of 10% and 30%. These initial data suggest some efficacy, especially for subjective outcome measures relative to baseline assessments and treatment with the vehicle, but larger studies are needed to confirm these effects.

Supplemental material available at https://www.ophthalmologyscience.org.

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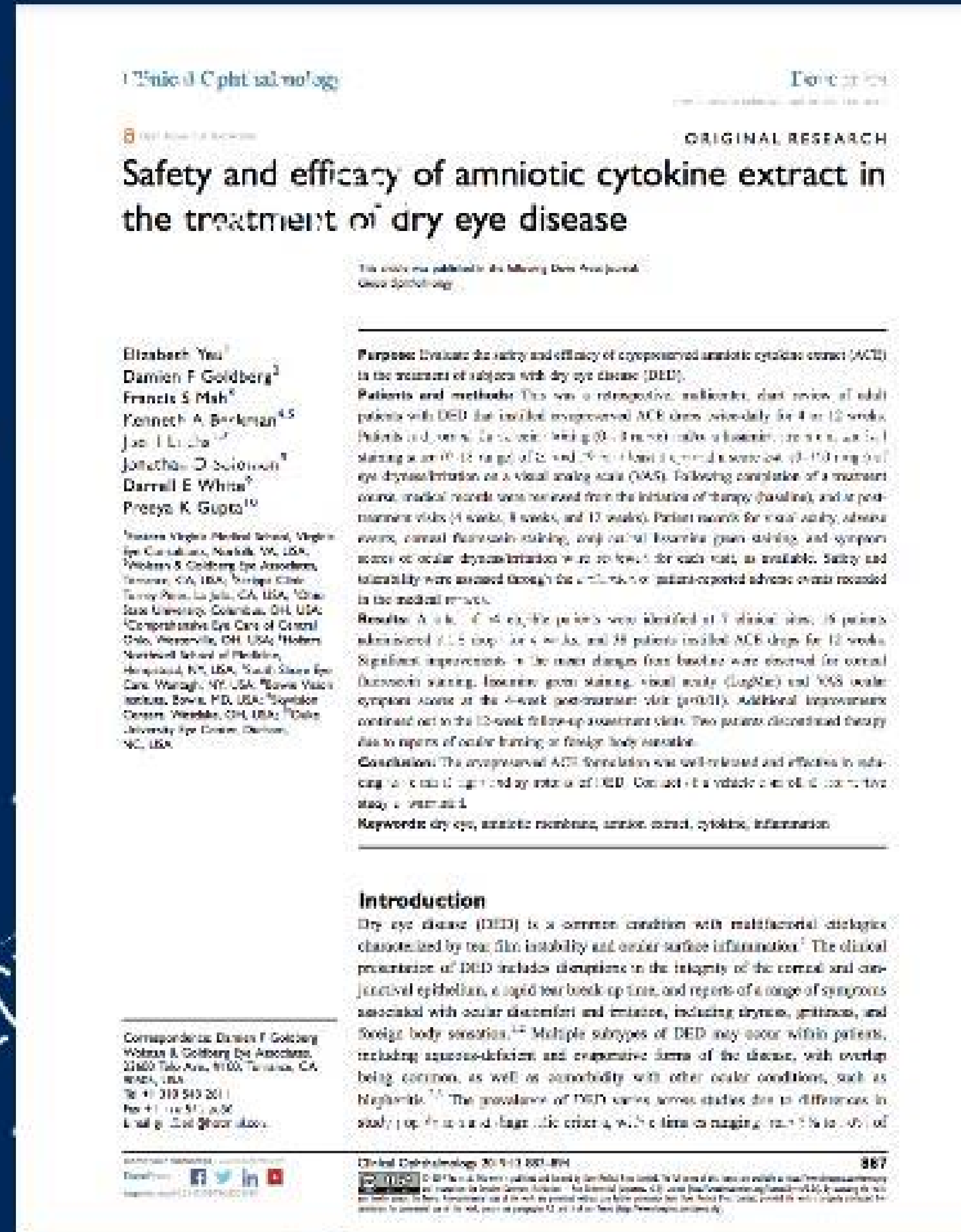
Amniotic cytokine extract

- Regenesol (BioTissue / Tissue Tech Inc.)
- Genesis ACE (Ocular Science)
- Regener-Eyes LITE (mild OSD) PRO (moderate-severe OSD) (Regenerative Processing Plant)

Key factors: prostaglandin E2 (PGE2), growth differentiation factor 11 (GDF11) thrombospondin-1, WNT4


Clinical Ophthalmology

ORIGINAL RESEARCH

Safety and efficacy of amniotic cytokine extract in the treatment of dry eye disease

Elizabeth Yeu
Damien F Goldberg
Francis S Mah
Kenneth A Beckman
Jonathan D Solomon
Darrell E White
Preeya K Gupta

Keywords: dry eye, amniotic membrane, amnion extract, cytokine, inflammation

Introduction

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JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS
Volume 34, Number 9, 2018

DOI: 10.1089/jop.2018.0015

ORIGINAL ARTICLE

Topical Treatment of Persistent Epithelial Defects with a Matrix Regenerating Agent

Mahmet Orkun Sevik, Semra Akkaya Turhan, and Ebru Toker

Type 1 DM

Herpetic NK

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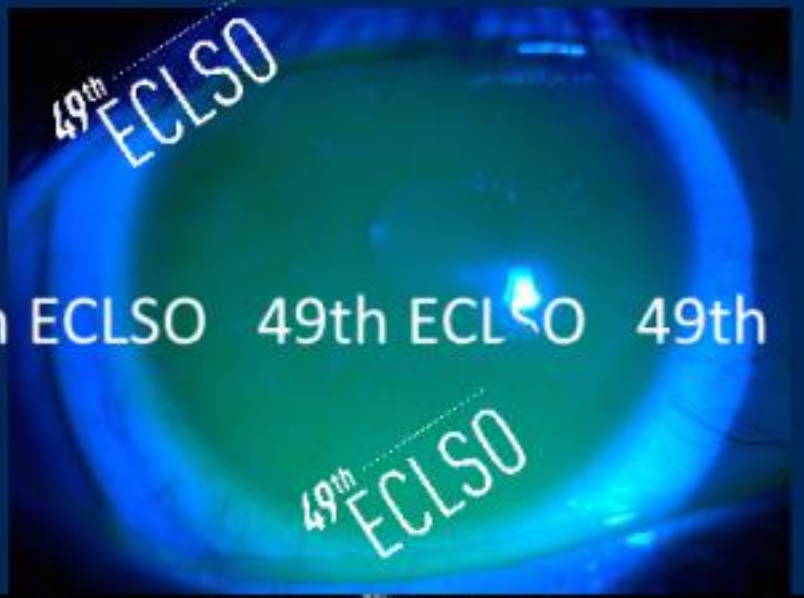
Insulin

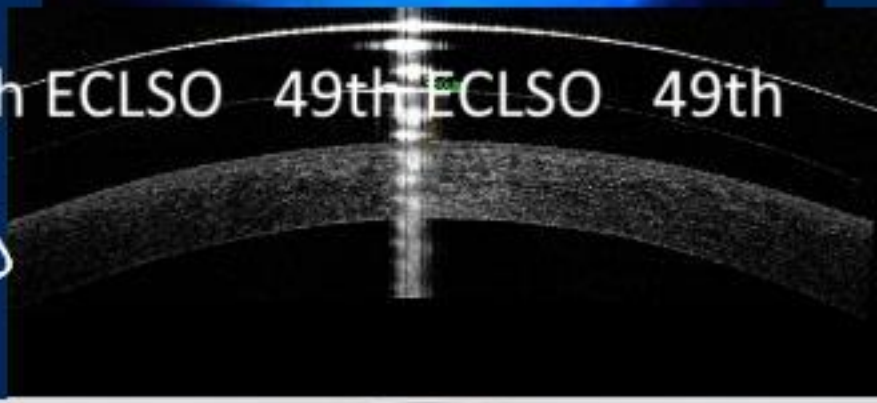
- Closely related to Insulin-like growth factor
- MOA is not clear-restoration of corneal nerves, improved epithelial cell migration ?
- 81%-100% complete healing of PEDs
  - Wang et al. Use of Topical Insulin to Treat Refractory Neurotrophic Corneal Ulcers. Cornea. 2017 Nov;36(11):1426-1428.
  - Diaz-Valle et al. Topical insulin for refractory persistent corneal epithelial defects. Eur J Ophthalmol. 2021 Sep;31(5):2280-2286.
- Faster healing compared to serum drops (32 days vs. 82 days)
  - Diaz-Valle D et al. Comparison of the efficacy of topical insulin with autologous serum eye drops in persistent epithelial defects of the cornea. Acta Ophthalmol. 2022 Jun;100(4):e912-e919
- 1 U/ml from regular insulin (100 U/ml) diluted in Systane

Scleral lenses

- Vault the cornea
- continuous hydration of cornea by post-lens fluid reservoir
- Preserve visual function
- Potential drug reservoir (serum tears, rhNGF)

- Schornack etal. Ophtlamol 2014; 121: 1398-405
- Witsberger & Schornack. Eye Contact Lens 2021; 47: 144-148

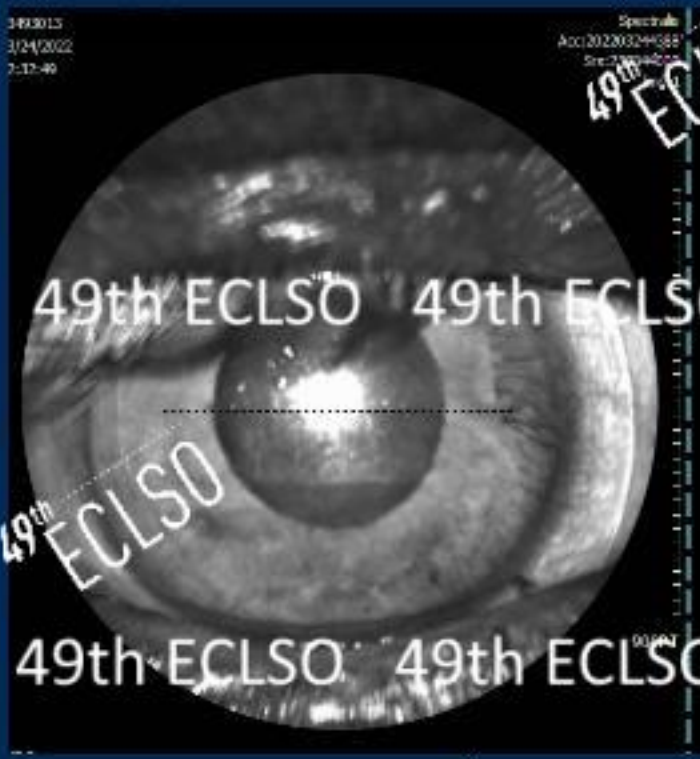


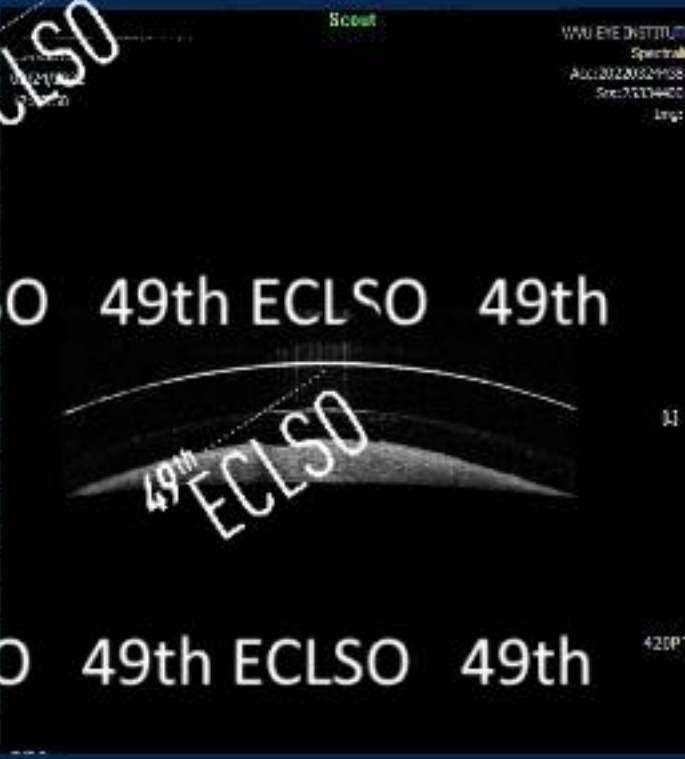


Corneo-scleral 12.9-14.9 mm

Mini-scleral 15-17.9 mm

Scleral 18-24 mm

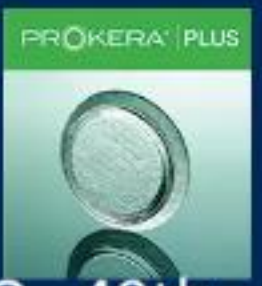


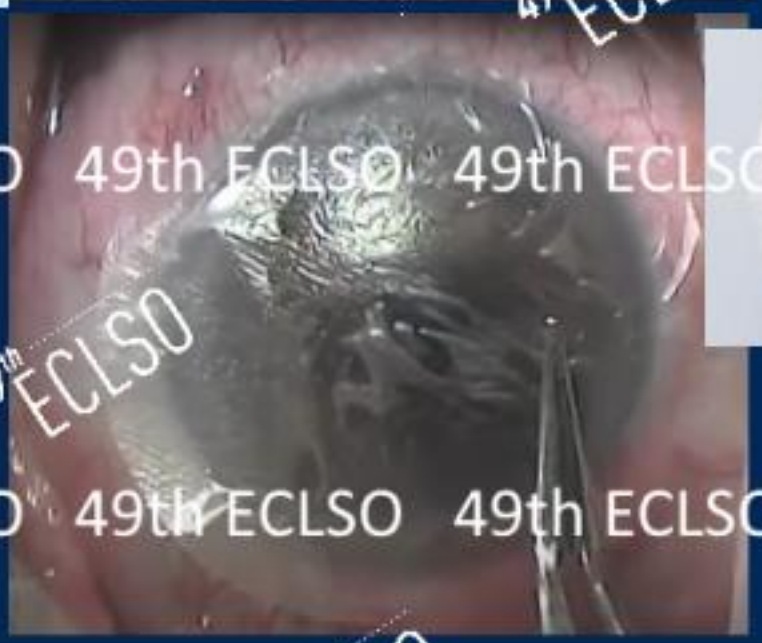


Uncontrolled DM, cicatrizing conjunctivitis undefined etiology (bx negative)
Serum tears, topical steroids, scleral lens, recently on Oxervate
VA OD CF improved to 20/100
VA OS HM improved to CF @ 5 ft

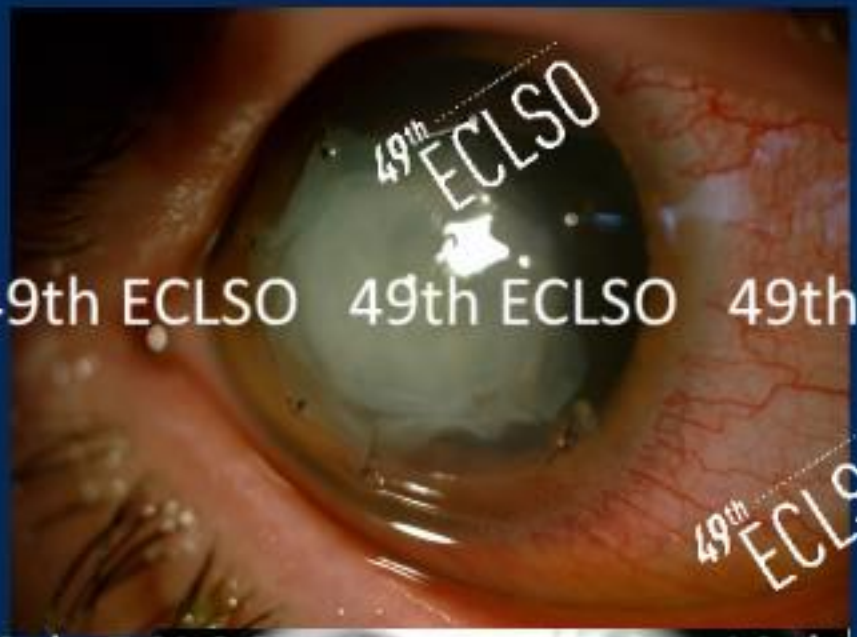
Amniotic membrane

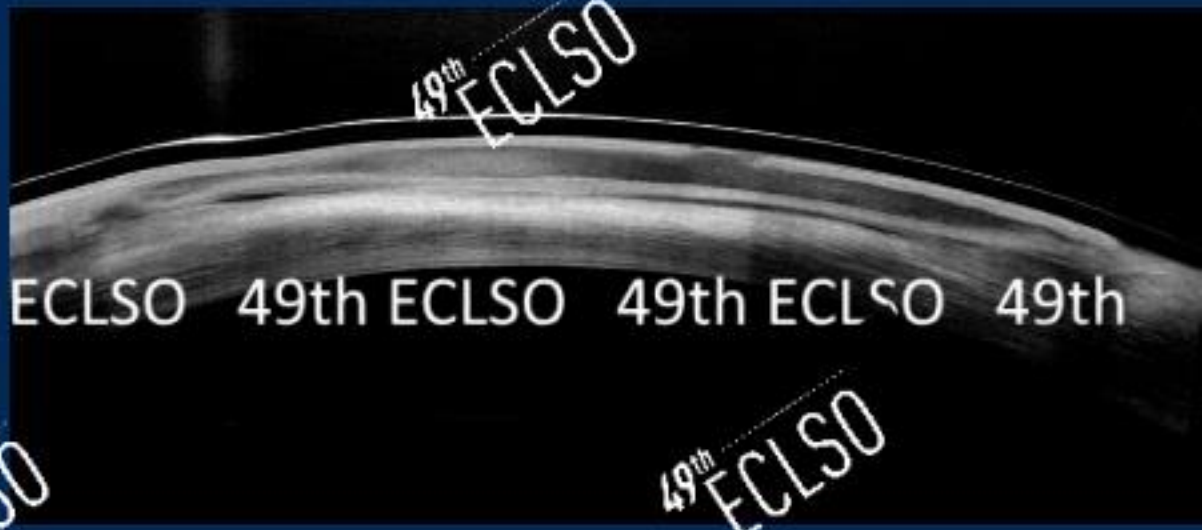
- Wet
  - Frozen
- Dry
  - Freeze dried
- Self-retaining
- Sutured

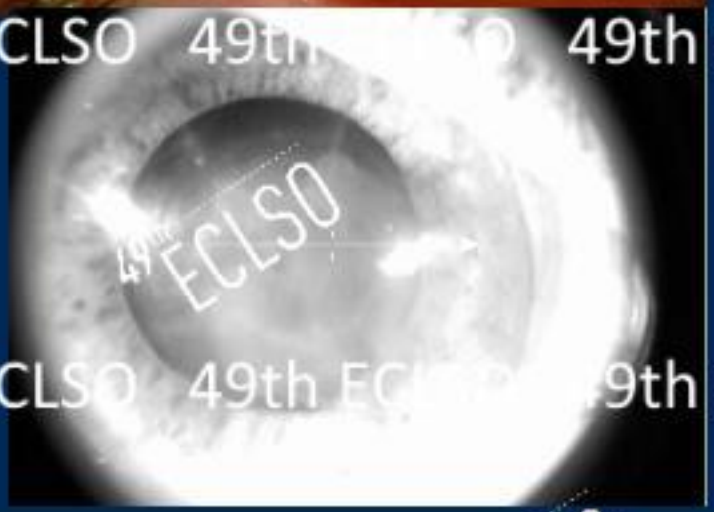


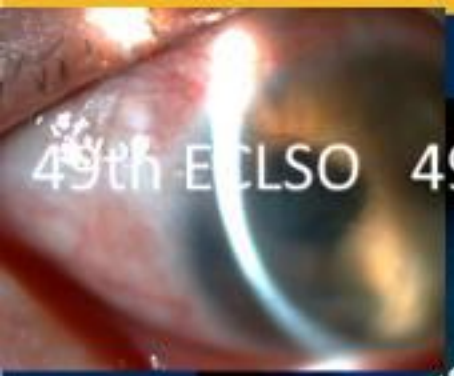


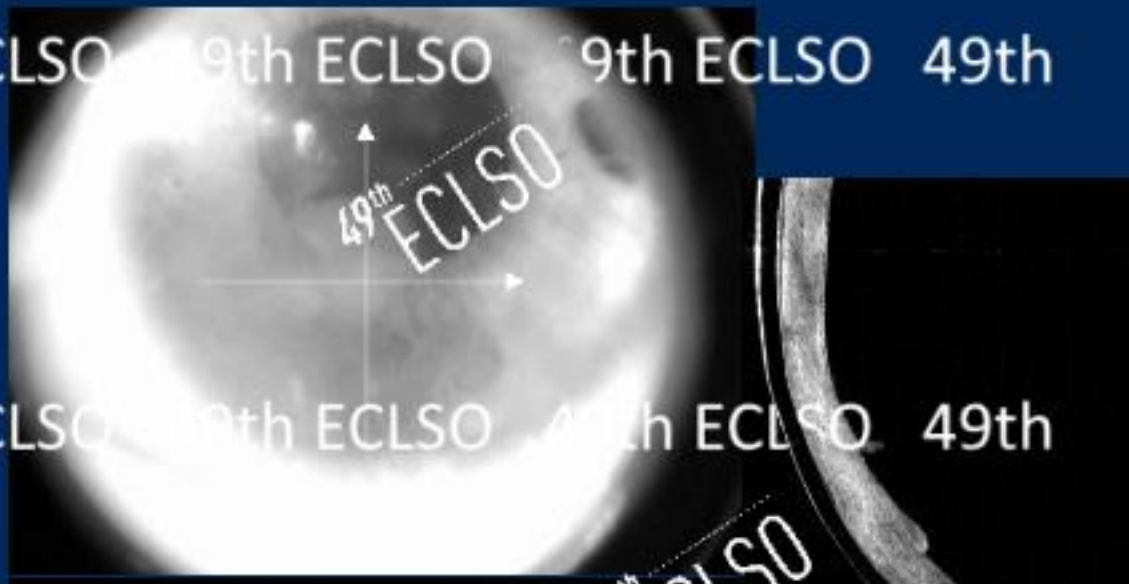
AMG + fibrin glue + sutures

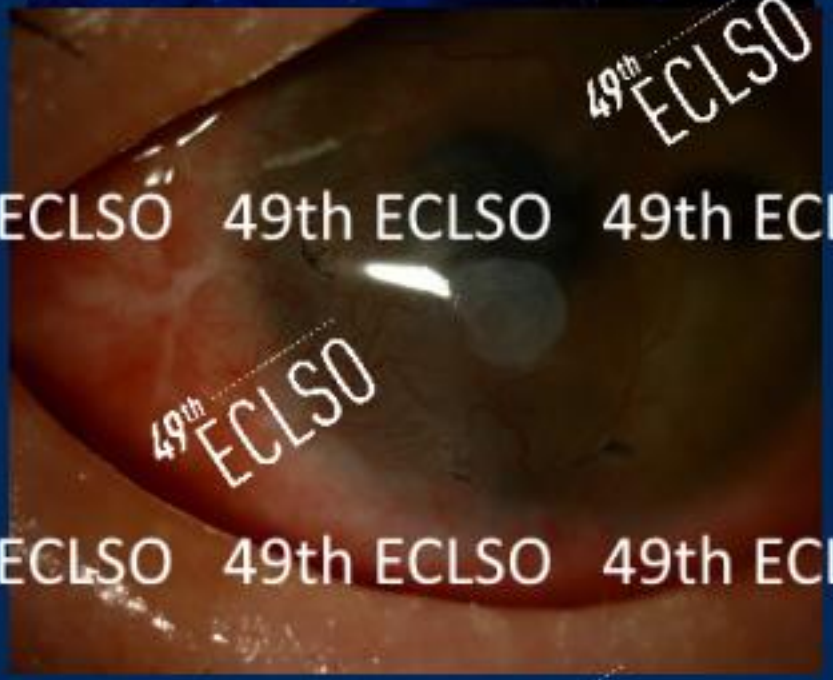












POH: Toxic epidermal necrolysis with extensive cicatrization, steroid induced galucoma, Trabeculectomy with MitC, bleb-related endophthalmitis, PPV, recurrent corneal ulcers,, scleral lens fittings, multiple AMG, PKP, failed graft

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TOPICAL TREATMENT WITH NERVE GROWTH FACTOR FOR CORNEAL NEUROTROPHIC ULCERS

ALESSANDRO LAMBIASE, M.D., PAOLO RAMA, M.D., STEFANO BONINI, M.D., GIANCARLO CAPRIOGLIO, M.D., AND LUIGI ALOE, PH.D.

ABSTRACT

Background Corneal neurotrophic ulcers associated with impairment of sensory innervation of the cornea may lead to loss of vision, and there is no effective treatment for these ulcers. We evaluated the effects of nerve growth factor in patients with this disorder.

Methods Twelve patients (14 eyes) with severe corneal neurotrophic ulcers associated with corneal anesthesia were treated with topical nerve growth factor 10 times daily for two days and then 6 times daily until the ulcers healed. Treatment continued for 2 weeks after the ulcers healed, and the patients were then followed for up to 15 months. The evolution of the corneal disease during treatment and follow-up was evaluated by slit-lamp examination, photography, fluorescein-dye testing, and tests of corneal sensitivity and best corrected visual acuity.

Results Corneal healing began 2 to 14 days after the initiation of treatment with nerve growth factor, and all patients had complete healing of their corneal ulcers after 10 days to 6 weeks of treatment. Corneal sensitivity improved in 13 eyes, and returned to normal in 2 of the 13 eyes. Corneal integrity and sensitivity were maintained during the follow-up period (range, 3 to 15 months). Best corrected visual acuity increased progressively during treatment and follow-up in all patients. There were no systemic or ocular side effects of treatment.

Conclusions In this preliminary, uncontrolled study, topically applied exogenous nerve growth factor restored corneal integrity in patients with corneal neurotrophic ulcers. (N Engl J Med 1998;338:1174-80.)

SEVERAL ocular and systemic diseases and circumstances, including fifth nerve palsy, viral infections, chemical burns, corneal surgery, abuse of topical anesthetics, neurotrophic keratitis, diabetes mellitus, and multiple sclerosis, can cause corneal neurotrophic ulcers.[1] These ulcers result from loss of the sensory innervation of the cornea, which leads to a decrease in the number of corneal [illegible] cells,[2] decreased metabolic and mitotic rates in the corneal epithelium (which increases cell permeability),[3,4] and reduced acetylcholine and choline acetyltransferase concentrations.[5] The result is progressive corneal damage, with epithelial defects, vascularization, opacification, ulceration, and ultimately, perforation, even in the absence of injury or infection. The standard treatments consist of covering the eye with a patch or a soft contact lens, tarsorrhaphy, and constructing a conjunctival flap, but they are often ineffective, and the outcome is often loss or severe impairment of vision.

Nerve growth factor is a well-characterized neurotrophin that is required for the development and survival of selected neurons, including sympathetic and sensory neurons.[6] It provides trophic support after neuronal injuries and reverses [illegible] changes induced by peripheral-nerve injury.[7] In denervated skin, nerve growth factor induces sensory-neuron sprouting and restores the density of nerve growth factor receptors.[8,9] Skin ulcers caused by the impairment of sensory innervation, such as in patients with diabetes mellitus and leprosy and after trauma, may be the result of decreased concentrations of local nerve growth factor.[10-12]

Nerve growth factor receptors have been found on the normal and abnormal cornea and conjunctiva.[13-15] In this study, we evaluated the efficacy of topical application of nerve growth factor in patients with severe noninfectious corneal ulcers due to corneal anesthesia that were unresponsive to conventional therapy.

METHODS

Patients

We studied 12 patients (14 eyes) who had noninfectious corneal ulcers associated with impaired corneal sensitivity, caused by essential neurotrophic keratitis (5 eyes), chemical burns (3 eyes), abuse of topical anesthetics (2 eyes), surgery for orbital tumor (1 eye), surgery for acoustic neuroma (1 eye), penetrating keratoplasty for unknown reasons (1 eye), and lamellar keratoplasty for a herpetic vascularized scar (1 eye) (Table 1). The mean age of the patients was 61 years (range, 4 to 86); six were female and six male. All the patients presented with corneal ulcer without ocular pain and photophobia or other signs of active inflammation (Fig. 1A). Corneal ulceration had been present for a mean (±SD) of 45±24 days. All had received conventional treatment, such as artificial tears and covering the eye with a patch or a soft contact lens,[1] and antibiotics with little or no benefit, and were referred to our center because of progressive worsening of the ulcer. The criteria for enrollment in the study were clinical evidence of corneal ulcer that was unresponsive to conventional therapy and the presence of corneal and conjunctival [illegible]. The [illegible]

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Topical Treatment with Nerve Growth Factor for Neurotrophic Keratitis

Stefano Bonini, MD,[1] Alessandro Lambiase, MD,[1,2] Paolo Rama, MD,[3] Giancarlo Caprioglio, MD,[3] Luigi Aloe, PhD[2]

Objective: To evaluate the efficacy of nerve growth factor (NGF) in patients with neurotrophic keratitis.

Design: Prospective, noncomparative, interventional case series.

Participants: Forty-five eyes of 43 consecutive patients with moderate (stage 2, n = 17) to severe (stage 3, n = 28) neurotrophic keratitis unresponsive to other nonsurgical therapies.

Methods: After a 10-day washout with preservative-free artificial tears, 45 eyes with neurotrophic keratitis received murine NGF (200 μg/ml) every 2 hours for 2 days followed by one drop six times daily until the ulcer healed. A maintenance dose of one drop NGF (100 μg/ml) was administered four times daily for the 2 weeks subsequent to ulcer healing.

Main Outcome Measures: Size and depth of the ulcer or the epithelial defect, corneal sensitivity, best corrected visual acuity, side effects, and relapse of the disease in the follow-up period.

Results: All patients had a complete resolution of the persistent epithelial defect (with or without an ulcer) after 12 days to 6 weeks of treatment with NGF. Patients affected by both stages of the disease demonstrated both improved corneal sensitivity and visual acuity ($P < 0.001$). No significant differences were observed in the time to complete corneal healing between stage 2 and stage 3 patients. Hyperemia and ocular and periocular pain were side effects reported during the first days of treatment. No relapse of the disease was observed during the follow-up period, with the exception of three patients with trigeminal nerve resection, who required a single retreatment.

Conclusions: Nerve growth factor eye drops improved corneal sensitivity and promoted corneal epithelial healing in both moderate and severe neurotrophic keratitis. Although performed in an uncontrolled and nonrandomized series of patients, this therapy shows promise for the restoration of ocular surface integrity and visual function in neurotrophic corneal disease. *Ophthalmology 2000;107:1347–1352* © *2000 by the American Academy of Ophthalmology.*

Neurotrophic keratitis is a degenerative corneal condition that results from a variety of ocular and systemic diseases such as fifth nerve palsy, viral infections, chemical burns, corneal surgery, abuse of topical anesthetics, diabetes mellitus, and multiple sclerosis.[1] In all of these diseases, a lesion of the trigeminal nerve occurs, resulting in impairment of corneal sensitivity and consequent degenerative changes to the corneal epithelium.[1,2] In fact, experimental and clinical studies have demonstrated that corneal nerve damage induces severe alterations in the metabolism and vitality of the epithelium, impairs epithelial healing, and is responsible for trophic ulcers.[1,2] The clinical stages of neurotrophic keratitis range from a punctate corneal keratopathy with tear film abnormalities (stage 1), to persistent epithelial defects (PED) without (stage 2) or with corneal ulcer (stage 3) [illegible], or melting and perforation.[2] Although [illegible] uncommon, [illegible] potentially devastating and may lead to blindness.

Persistent epithelial defects and corneal ulcers such as those occurring in neurotrophic keratitis are known to often be unresponsive to different therapeutic approaches including tarsorrhaphy or patching, unpreserved artificial tears, or soft contact lens bandage.[3,4] Other surgical measures, namely amniotic membrane transplantation, may be promising if recently published results are confirmed in future studies.[5]

Nerve growth factor (NGF) is a polypeptide discovered in the early 1950s by R. Levi-Montalcini. It is essential for the survival and growth of sympathetic and sensory neurons and for differentiation of neurons in the central nervous system.[6] Nerve growth factor induces neurite sprouting by neural cells and restores the function of injured neurons.[6-8] A variety of tissues and cell types produce and release NGF, and specific high-affinity and low-affinity NGF receptors have been identified on cell membranes of innervating cell populations, including the ocular surface.[9-11]

In a preliminary study, we recently reported that topical

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rhNGF -Cenegermin–bkbj

Oxervate, Dompé

- Recombinant form of human nerve growth factor
- Produced by
  - Isolating the gene sequence responsible for human NGF
  - Introducing these genes in plasmids into E.Coli
  - Gene product is collected
- Role of NGF
  - Regeneration and survival of corneal nerves
  - Proliferation, differentiation and survival of epithelial cells
  - Tear production by lacrimal gland via binding to receptors on lacrimal glands
  - Promotion of sensory-mediated tear secretion through activation of reflex arcs

Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

Stefano Bonini, MD,[1] Alessandro Lambiase, M[illegible]
Marcello Allegretti, PhD,[3] Wendy Chan, PhD,[3]

REPARO (NGF021

8-week Controlled Treatment
One drop, administered 6 times daily

OXERVATE 20 mcg/mL[1]	n=52
Cenegermin 10 mcg/mL	n=52
Vehicle	n=52

REPARO (NGF0212)
OXERVATE 20 mcg/mL[1] (n=52)
Vehicle (n=52)

NGF0214
OXERVATE 20 mcg/mL[1] (n=24)
Vehicle (n=24)

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

A Multicenter Randomized Vehicle-Controlled Pivotal Trial

Victor L. Perez, MD,[2] Fahran Hamrah, MD,[4]
Stephen Foster, MD,[5,6] John Affeldt, MD,[7]
[illegible], PhD,[7] Marcello Allegretti, PhD,[7]

ted States, n=49)

Study Visits

[illegible]

Primary Efficacy
Measured at Week 8
Complete healing of the
persistent epithelial defect or
[illegible]
[illegible]
o other persistent staining).

Follow-up
at Week 24

80% of patients who healed after one 8-week course of treatment remained healed at 48 week f/u

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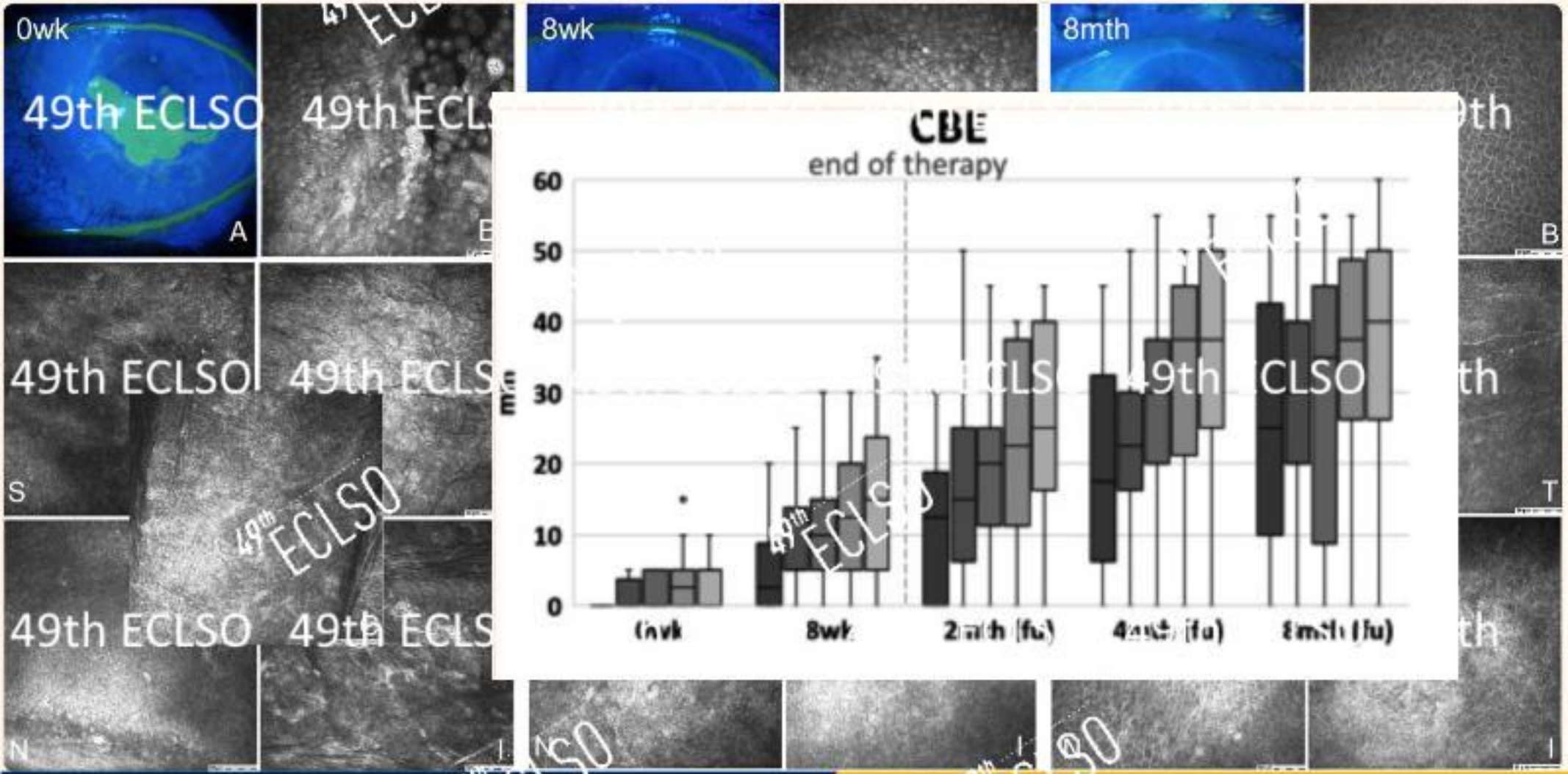
PMCID: PMC8862484
PMID: 35189948

Eight months follow-up of corneal nerves and sensitivity after treatment with cenegermin for neurotrophic keratopathy

Emilio Pedrotti,[1] Erika Bonacci,[1] Chiara Chierego,[1] Alessandra De Gregorio,[2] Tiziano Cozzini,[2][1] Tommaso Brinberti,[1] Grazia Caldarella,[1] Giovanlorenzo Pastore,[1] Adriano Fasolo,[1,3] and Giorgio Marchini[1]



How to use

- Approved by EMA, EU (2017), FDA (2018, approved for all stages)
- 6 X per day for 8 weeks
- Discontinue steroids and topicals w/ preservatives
- Do not use in active infection
- Remove CL's before use

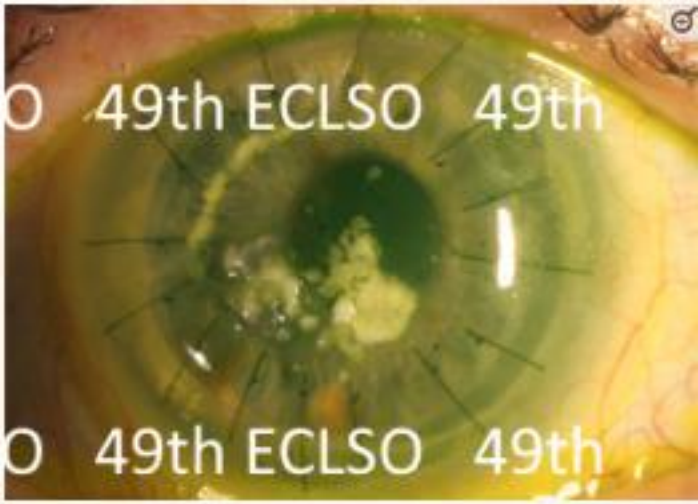
Follow-up:

- A second round of tx may be tried in failures

Adverse effect:

- Eye pain (16 %)
- Hyperemia, lacrimation, foreign body sensation, corneal deposits (10 %)

oxervate™ 0.002% (20 mcg/mL)
(cenegermin-bkbj) ophthalmic solution



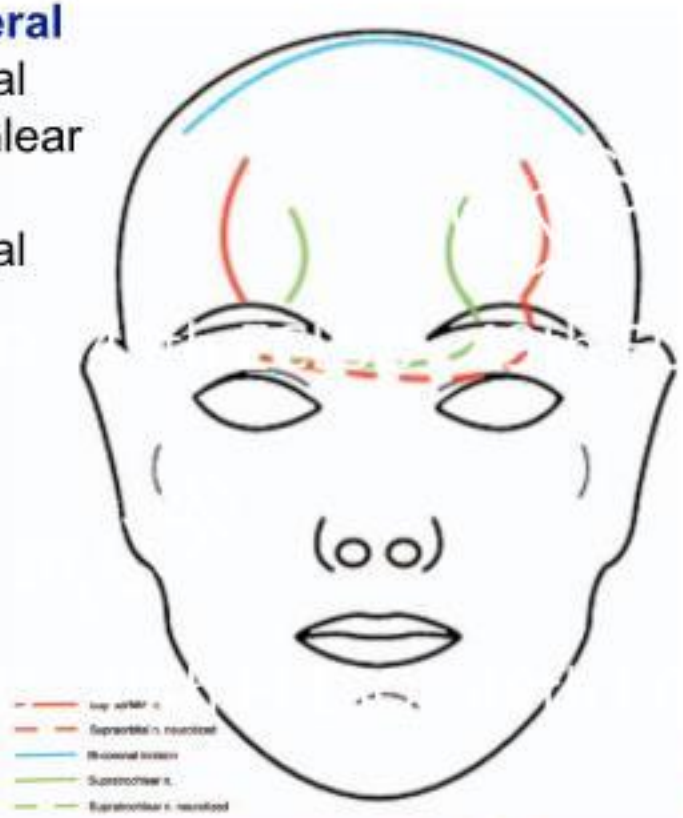
White CA, Affeldt J. Am J Ophthalmol Case Rep. 2022 May 14;27:101584.

Corneal neurotization

- Transfer of a healthy nerve segment to the corneo-limbal area to reinnervate a desensitized cornea

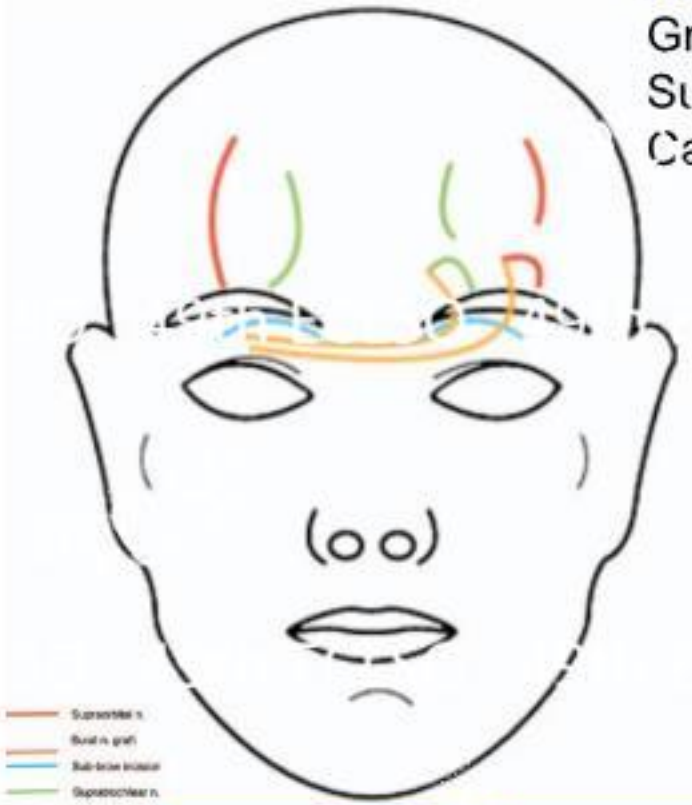
Direct CN

Contralateral
Supraorbital
Supratrochlear
Ipsilateral
Supraorbital
Infraorbital



Indirect CN

Nerve conduit
Greater auricular n
Sural nerve
Cadaveric Allografts



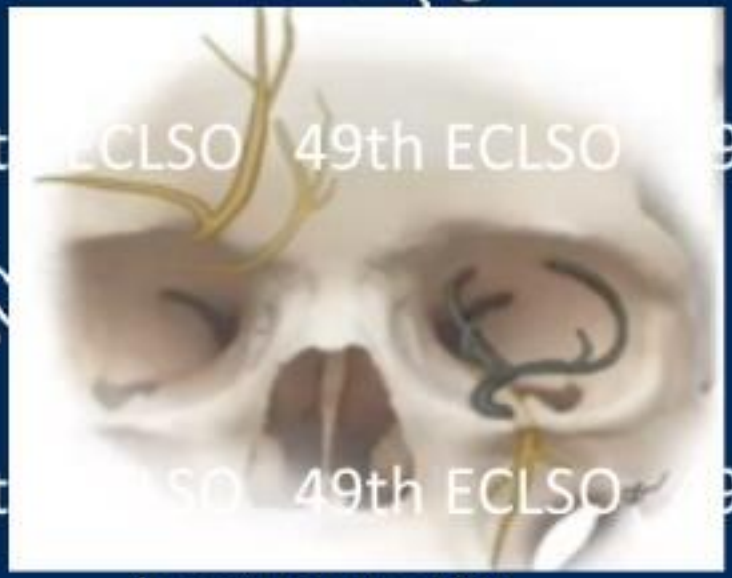
Terzis, Dryer, Bodner. Plast Reconstr Surg 123: 112 (2009)

Dr. Mauger-Cornea

Dr. Nyugen-Oculoplastics

Dr. Thuro-Oculoplastics

Contralateral indirect CN



İpsilateral indirect CN

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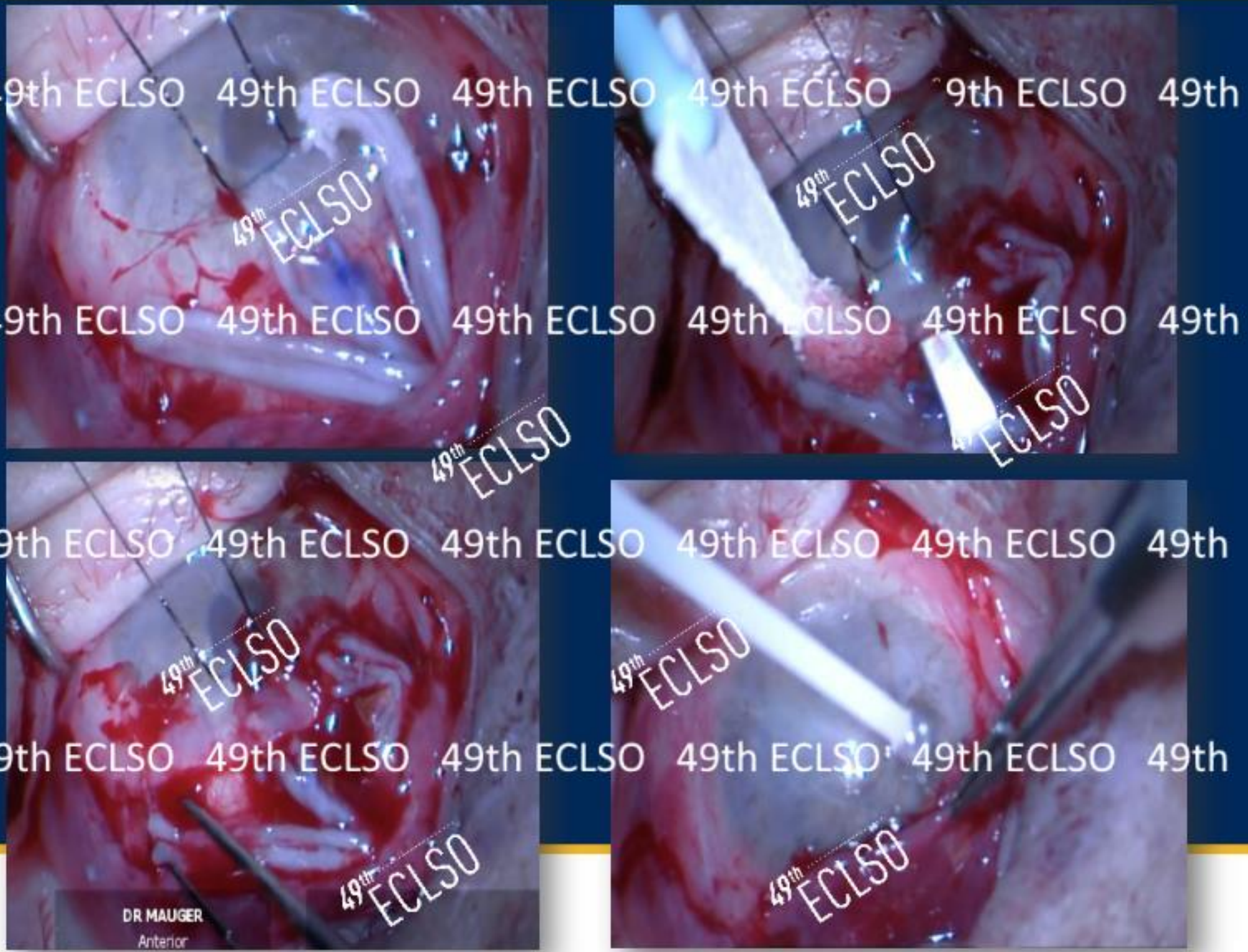
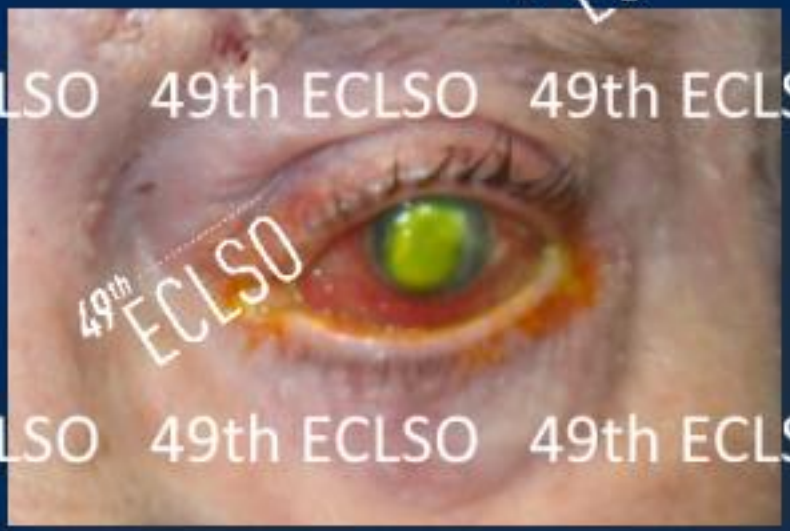

49th ECLSO
DR MAUGER
Anterior

Our results……

	Age	Etiology	Technique	Follow-up	CBE preop (mm)	CBE postop (mm)	VA preop	VA postop
Pt 1	75	HZO, uncontrolled DM	Allograft contralateral supra-orbital	7.5 months	0	0.5	HM	CF
Pt 2	5	Brainstem astrocytoma Stereotactic surgery CN V,VI,VII palsy Corneal ulcer PK for perforation	Allograft contralateral supraorbital	6.5 months	0	0	LP	CF
Pt 3	72	DM stage 3 NK	Allograft ipsilateral supraorbital	8 weeks	0	0.5	LP	LP
Pt 4	84	HZO, failed PK	Direct ipsilateral infraorbital	8 weeks	0	6	20/400	20/40 0
Pt 5	62	Meningioma sx	Allograft contralateral supra-orbital	6 weeks	0	0	HM	20/20 0

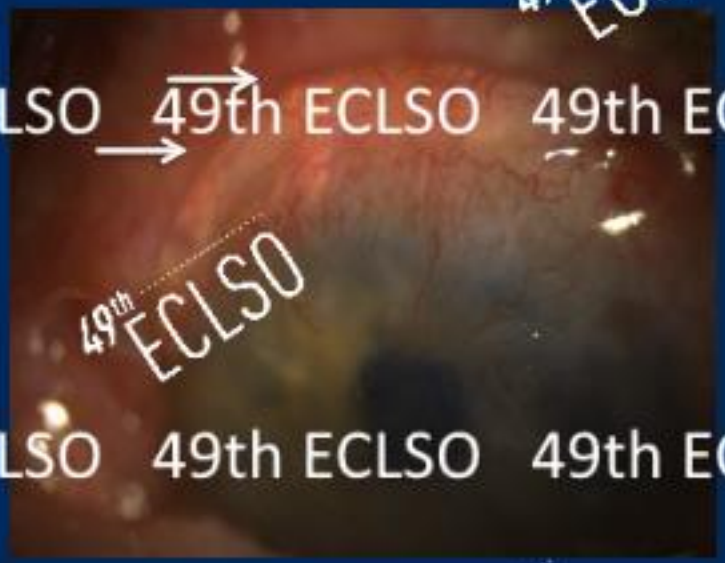
What to expect after CN

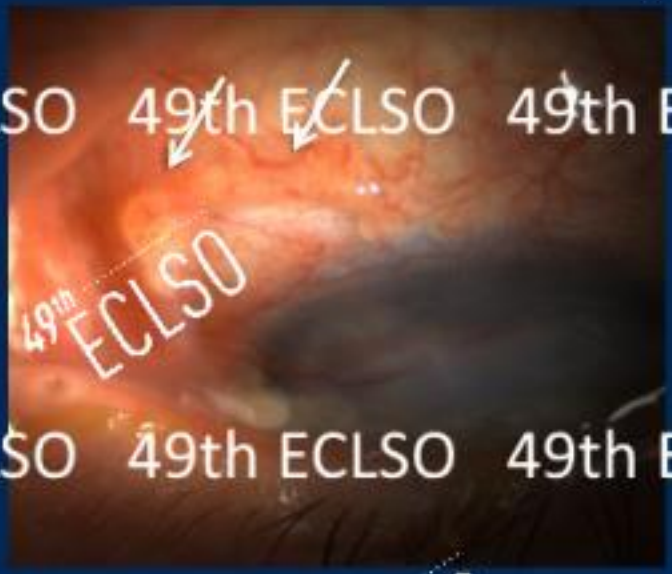
- Corneal sensitivity recovers in 8-9 mos
  - Park JK et al. OPRS 2020
- Recovery of corneal esnsitivity may take longer in indirect technique
- IVCM nerve regeneration precedes recovery of CS
  - Fung SSM et al. Cornea 2018
- limited visual gain in deep stromal scars



Corneal neurotization

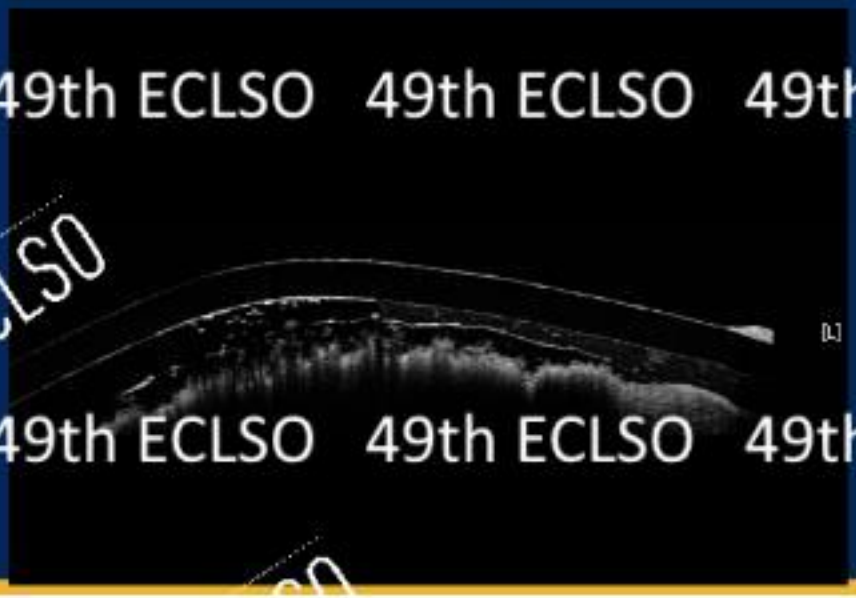
- viable option in earlier stages NK with central causes of denervation
- Adjuvant therapy with topical rhNGF can potentiate its outcomes
- Potential to improve prognosis of future optical PK





Stage 3 Management

- Multilayered AMG
- Conjunctival flaps
- Perforations
  - AMG+ fibrin glue
  - Cyanoacrylate glue
  - Corneal grafts



In Summary

- Neurotrophic keratitis is a sight-threatening corneal pathology associated with impaired trigeminal innervation
- Management of NK can be very challenging.
- Successful management depends on early recognition
  - Awareness and corneal sensitivity testing
- Topical rhNGF is a breakthrough therapy in NK management
- Corneal neurotization is a still evolving, but promising surgical option which can offer a permanent cure to NK.

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Thank you for your attention…..