What You Should Know About Neurotrophic Keratitis

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Disclosures

- Dompè: R
- Santen: C

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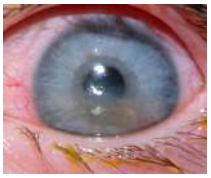
What is neurotrophic keratitis?



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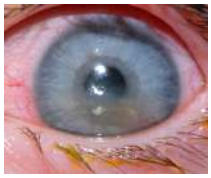

- AAO EyeWiki:
  - Neurotrophic Keratitis (NK) is a corneal degenerative disease characterized by a reduction or absence of corneal sensitivity. In NK, corneal innervation by the trigeminal nerve is impaired.

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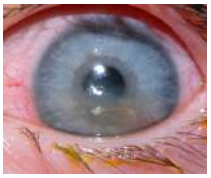
What is neurotrophic keratitis?



- Dua et al 2018:
  - Neurotrophic keratopathy is a disease related to alterations in corneal nerves leading to impairment in sensory and trophic function with consequent breakdown of the corneal epithelium, affecting health and integrity of the tear film, epithelium and stroma.

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Dua et al. *Prog Retin Eye Res*, 2018.

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Discovery of NK

- 1822 Mayo: V section > corneal anesthesia
- 1854 Graefe: first human case
- 1866 Rosow & Snellen: rabbit experiment
  - Corneal changes reverse on complete lid closure
  - Termed *keratitis neuroparalytica*

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Mayo. *Anatomical and Physiological Commentaries*, 1822.
Graefe. Archiv für Ophthalmologie, 1854.
Snellen. Dutch Archives of Medicine and Philosophy, 1866.

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Prevalence & Incidence of NK

orphanet

- Prevalence: 1 - 5/10,000
- Incidence:
  - Sacchetti & Lambiase 2014: <1.6 / 10000
  - Labetoulle et al 2005: 6% of herpetic keratitis
  - Dworkin et al 2007: 12.8% of zoster keratitis
  - Bhatti & Patel 2005: 0.02 / 10000 neurosurgical op
  - Rare but devastating: 15% amniotic membrane
    40% tectonic keratoplasty

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Sachetti & Lambiase. *Clin Ophthalmol*, 2014.
Labetoulle et al. *Ophthalmology*, 2005.
Dworkin et al. *Clin Infect Dis*, 2007.
Bhatti & Patel. *Curr Opin Ophthalmol* 2005.

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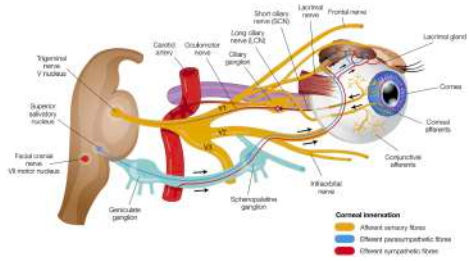
NK & Corneal innervation



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Dua et al. *Prog Retin Eye Res*, 2018.
Stern et al. *Int Rev Immunol*, 2013.

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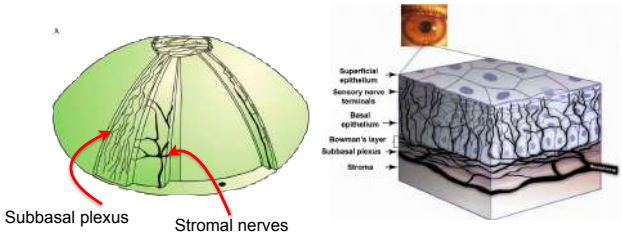
NK & Corneal innervation



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Müller et al. *Exp Eye Res*, 2003.

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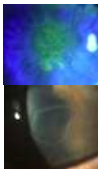
Etiology of neurotrophic keratopathy

- Systemic
  - **Diabetes**, Leprosy, Vit A deficiency, Amyloidosis, MS
- CNS
  - **Surgery**, **Trauma**, Neoplasm, Aneurysm, CVA
- Ocular
  - **Herpetic** infections, Acanthamoeba
  - **Chemical:** burns, anesthetics abuse, toxicity (NSAID)
  - **Surgery:** grafting, refractive laser, SMILE, CXL, laser & PPV in DR, diode



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Etiology of neurotrophic keratopathy

- Congenital/ Genetic

1. **Isolated corneal involvement**

2. Ocular syndromes
   - Lattice
   - Macular
   - Fleck
   - Schnyder
   - Contralateral anophthalmos and microsomia

3. **Isolated trigeminal insensitivity**
   - Familial
   - Sporadic

4. Neurological syndromes
   - Wallenberg
   - **Möbius**
   - **Riley-Day**
   - **Pontine Tegmental Cap Dysplasia**
   - Generalized insensitivity to pain & weakness
   - Cerebellar ataxis, cogwheel ocular pursuits, anal atresia, and abnormal OKN

5. Systemic syndromes
   - MURCS
   - **Goldenhar**
   - VACTERL association
   - Hypohidrotic ectodermal dysplasia

6. **Congenital insensitivity to pain**
   - Without anhidrosis (CIP)
   - With anhidrosis (CIPA/ HSAN IV)

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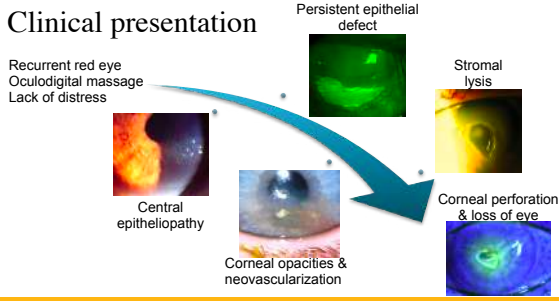
Clinical presentation



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Müller et al. *Exp Eye Res*, 2003.
Dua et al. *Prog Retin Eye Res*, 2018.

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Mackie's classification

Stage 1 of neurotrophic keratopathy demonstrates the following:

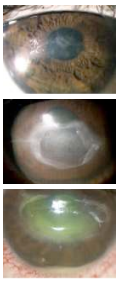
- Rose Bengal staining of the inferior palpebral conjunctiva (lissamine green is now the standard dye used instead of rose Bengal)
- Decreased tear breakup time
- Increased mucous viscosity
- Punctate corneal epithelial fluorescein staining

Stage 2 is characterized by:

- Epithelial defect - Usually oval and in the central/superior cornea
- Defect surrounded by a rim of loose epithelium
- Edges may become smooth and rolled
- Stromal swelling with folds in the Descemet's membrane
- Sometimes associated with anterior chamber inflammatory activity

Stage 3 is characterized by:

- Stromal lysis/melting
- May result in perforation



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Sacchetti & Lambiase. *Clin Ophthalmol*, 2014.
Dua et al. *Prog Retin Eye Res*, 2018.
Mackie. *Current Ocular Therapy*, PA 1995.

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Dua et al. *Prog Retin Eye Res*, 2018.
Mackie. *Current Ocular Therapy*, PA 1995.

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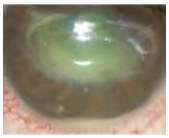

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Sacchetti & Lambiase. *Clin Ophthalmol*, 2014.
Dua et al. *Prog Retin Eye Res*, 2018.
Mackie. *Current Ocular Therapy*, PA 1995.

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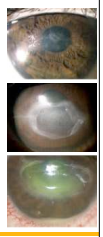
ASCRS NKSG

Stage		Clinical features
Mackie	ASCRS	
	0	Altered sensation without any keratopathy
1	1	Corneal epitheliopathy without any stromal involvement
	2	Punctate epithelial keratopathy with anterior stromal haze
2	3	Persistent or recurrent epithelial defects
	4	Persistent or recurrent epithelial defects with stromal scarring but no ulceration
	5	Persistent or recurrent epithelial defects with corneal ulceration
3	6	Corneal perforation



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Sacchetti & Lambiase. *Clin Ophthalmol*, 2014.
Dua et al. *Prog Retin Eye Res*, 2018.
Mackie. *Current Ocular Therapy*, PA 1995.

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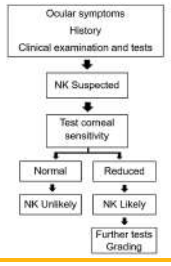
Diagnosing neurotrophic keratopathy



- Symptoms
  - Asymptomatic
  - Dryness
  - Lacrimation
  - Reduced vision
  - Disproportionate with signs

Painless infective keratitis

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Image courtesy of SickKids Hospital, Toronto, Canada
Dua et al. *Prog Retin Eye Res* 2018.

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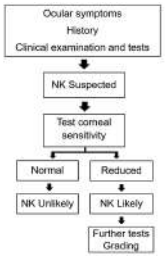
Diagnosing neurotrophic keratopathy



- Symptoms
- History:
  - Underlying eye/ systemic condition
  - Previous ocular/brain surgery

Dua et al. *Prog Retin Eye Res* 2018.

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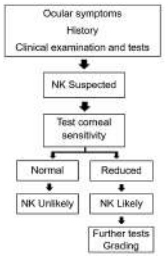
Diagnosing neurotrophic keratopathy



- Symptoms
- History
- Exam
  - Cranial nerves
  - External exam: mind the white eye
  - Slit-lamp exam: cornea & AC
  - Corneal sensation testing

Dua et al. *Prog Retin Eye Res* 2018.

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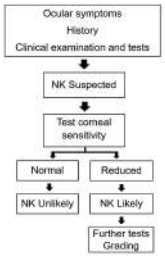
Diagnosing neurotrophic keratopathy



- Symptoms
- History
- Exam
- Investigations
  - ±MRI brain and orbit
  - IVCM

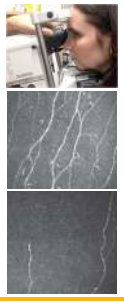


Image from European Dry Eye Network.
Dua et al. *Prog Retin Eye Res*, 2018.
Cruzat et al. *Semin Ophthalmol*, 2010

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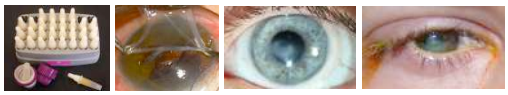
Overview of conventional treatment

- Stabilize corneal epithelium
- Encourage healing
- Prevent stromal lysis



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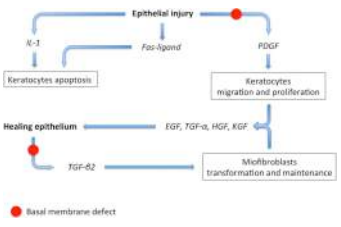
Promoting healing: growth factors substitutes



Spadea et al. *Br J Ophthalmol*, 2016.
Tsubota et al. *Ophthalmology*, 1999.

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Serum drops in neurotrophic keratopathy

- Matsumoto et al 2004
  - 14 eyes of 11 patients with NK (7 DM, 5 herpetic)
  - 20% autologous serum 5 - 10x/day
  - All healed in 17.1±8.0days
  - Improved corneal sensitivity
- Yoon et al. 2007
  - 20% umbilical cord blood serum
  - 28 eyes healed at 4.4±4.0weeks
- Jeng & Dupps 2009
  - **50% autologous serum -**
    23/25 eyes healed in 22.4 ± 26.1 days

Matsumoto et al. *Ophthalmology*, 2004.
Yoon et al. *Ophthalmology*, 2007.
Jeng & Dupps. *Cornea*, 2009.

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Amniotic membrane in neurotrophic keratopathy

- Chen et al. 2000
  - 16 eyes of 15 patients with NK
  - 76% healed within 16.6±9.0 days
  - Others healed after tarsorrhaphy added
- Khokhar et al. 2005
  - RCT of 30 eyes of 30 patients
    - Grp 1: conventional + tarsorrhaphy or BCL
    - Grp 2: amniotic membrane transplant
    - Complete healing at 3 month f/u at end point
  - No difference in healing response (success or time to healing)

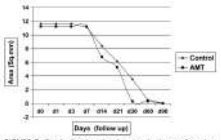

FIGURE 5. Graph showing the decrease in the median ulcer area in the two groups during the study period of 90 days.

Chen et al. *Br J Ophthalmology*, 2000.
Khokhar et al. *Cornea*, 2005.

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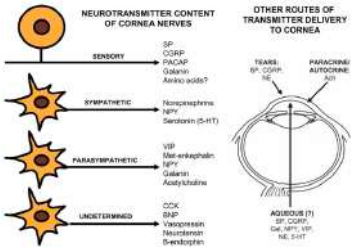
Novel interventions in NK



Müller et al. *Exp Eye Res*, 2003.

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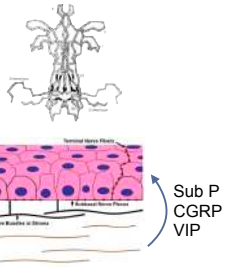
Neurotrophins

- Family of 4
  - **Nerve growth factor (NGF)**
  - Neurotrophin 3 (NT-3)
  - Neurotrophin 4/5 (NT-4)
  - Brain-derived neurtrophic factor (BDNF)



Müller et al. *Exp Eye Res*, 2003.
Belmonte et al. *Ocul Surf*, 2017.
Dua et al. *Prog Retin Eye Res*, 2018.

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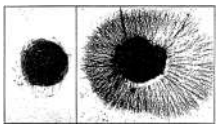
NGF

- First discovered by Levi-Montalcini & Cohen 1954
  - Discovered factor that stimulated nerve growth from sarcoma
  - Shown to stimulate nerve growth in chick embryo
  - Nobel Prize Awardees in 1986




Rita Levi-Montalcini


Stanley Cohen

Images from www.nobelprize.org.
Cohen et al. *Proc Natl Acad Sci*, 1954.

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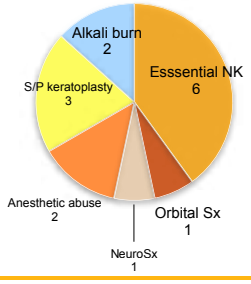
NGF and NK

- Lambiase et al. 1998
  - 14 eyes of 12 patients
  - Persisting ulcer for 45±24days
  - No sensation on cotton wisp
  - Murine NGF 200µg/ml 10x/day



Lambiase et al. *NEJM*, 1998.

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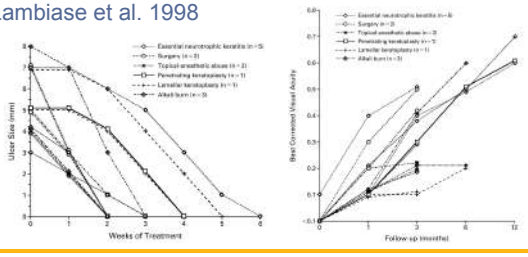
NGF and NK

- Lambiase et al. 1998



Lambiase et al. *NEJM*, 1998.

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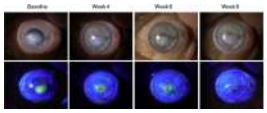
Cenegermin & NK

- REPARO Trial
  - Phase 1 and 2 multi-center double-blind RCT
  - rhNGF (Cenegermin) in 10 or 20µg/ml, 6x/day x 8weeks
  - Patients aged ≥18 with Mackie stage 2 or 3 NK

Table 2. Primary Efficacy Analysis of Corneal Healing (<0.5-mm Lesion Staining)

Results	Recombinant Human Nerve Growth Factor	
	10 µg/ml (N = 321)*	20 µg/ml (N = 321)*
Healed at week 4, no. (%)	28/51 (54.9)	29/50 (58.0)
Difference (rhNGF − vehicle), %	15.3	18.4
97.06% CI	15.88–54.71	18.96–57.81
P value	<0.001	<0.001
Healed at week 8, no. (%)	38/51 (74.5)	37/50 (74.0)
Difference (rhNGF − vehicle), %	31.4	32.9
97.06% CI	11.25–51.49	10.60–51.13
P value	0.001	0.002



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Bonini et al. *Ophthalmology*, 2018.

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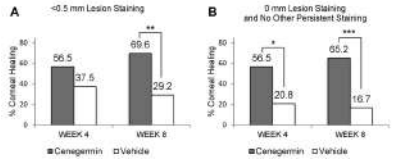
Cenegermin & NK

- US Pivotal trial, 2020
  - 11 US centers double-blind RCT, N=48
  - Placebo v Cenegermin 20µg/ml
  - 24 weeks follow-up

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

A Multicenter Randomized Vehicle-Controlled Pivotal Trial



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Pflugfelder et al. *Ophthalmology*, 2020.

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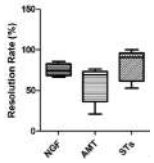
Cenegermin & NK

- Zwingelberg et al., 2020
  - N=11, f/u 13.6months, 100% PED closed
  - 1/11 recurred at 9months after treatment
- Hatcher et al., 2021
  - 9 eyes in 8 children, f/u 2-13months
  - 63% improved NK staging
  - mean recurrence free 10months
- Di Zazzo et al., 2019
  - Treatment comparison



Treatment	Eyes (n)	Healing %
NGF	132	75.2 ± 4
AMT	124	57.6 ± 21.38
STs	107	81.2 ± 19.2
BCL	16	66.7 ± 0.7

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Zwingelberg et al. *Klin Monatsbl Augenheilkd* 2020.
Hatcher et al. *Ocul Surf*, 2021.
Di Zazzo et al. *Ocul Surf*, 2019.

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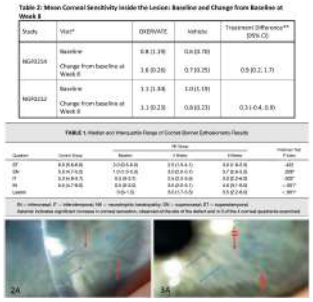
Cenegermin & NK

- Heterogenous cohort
  - Disease specific efficacy unknown
  - Lack of data on stage 1 NK
- Corneal sensitivity
  - Conflicting data
- Side effect profile
  - Ocular pain (16%)
  - Hyperemia, FBS, inflammation
  - Neovascularization - variable



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FDA Printed labeling
Mastropasqua et al. *Am J Ophthalmo*, 2020
Zwingelberg et al. *Klin Monatsbl Augenheilkd* 2020

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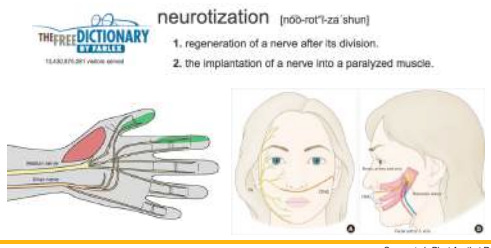
Novel surgery in NK - corneal neurotization



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Sassu et al. *Plast Aesthet Res*, 2015.
Leckenby & Grobbelaar. *Arch Plast Surg*, 2013.

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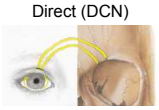
Types of corneal neurotization

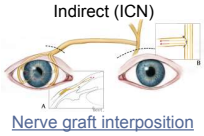
Direct (DCN)



Direct transfer of a healthy nerve

- Contralateral transfer
- Ipsilateral transfer
- Endoscopic contralateral transfer
- Endoscopic ipsilateral transfer

Indirect (ICN)



Nerve graft interposition

- Sural nerve → frontal branches
- Great auricular nerve → frontal branches
- Sural nerve → greater auricular nerve
- Acellular nerve allograft

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Image courtesy of Farheen Ali.
Terzis et al. *Plast Reconstr Surg*, 2009.

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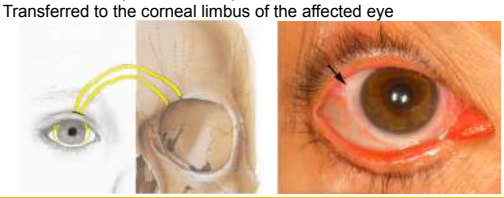
Direct corneal neurotization

- Terzis et al. 2009:
  - Contralateral supraorbital & supratrochlear nerves
  - Transferred to the corneal limbus of the affected eye



Terzis et al. *Plast Reconstr Surg*, 2009.

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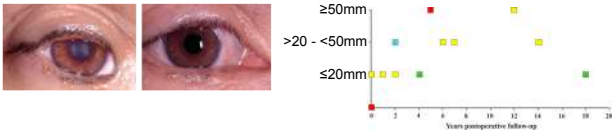
Direct corneal neurotization

- Terzis et al. 2009:
  - 6 patients with unilateral NK



Terzis et al. *Plast Reconstr Surg*, 2009.

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Indirect corneal neurotization

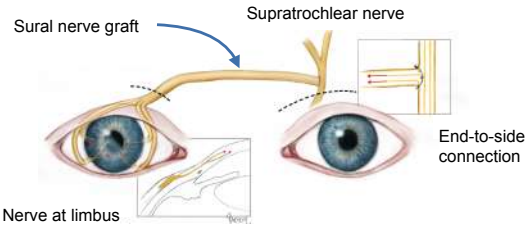

Image courtesy of Farheen Ali.

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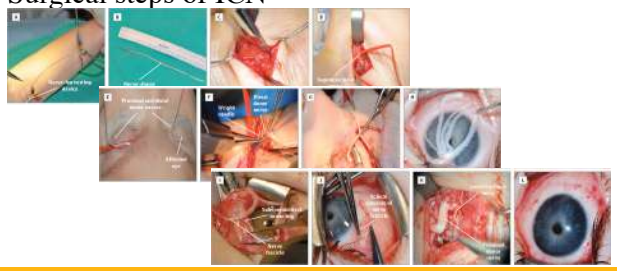
Surgical steps of ICN



Elbaz et al. *JAMA Ophthalmol*, 2014.

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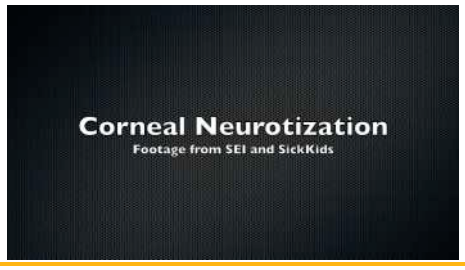
Indirect corneal neurotization



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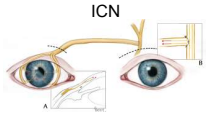
Outcomes of corneal neurotization

DCN

Direct transfer of a healthy nerve

- No. of patients: 26
- Median age: 43 years (19 - 81)
- Median f/u: 2 years (0.25 - 19)
- Sensation imp: 21 (81%)
- Vision imp: 8 (67%)

ICN



Nerve graft interposition

- No. of patients: 73
- Median age: 30 years (0 - 76)
- Median f/u: 1.0 years (0.13 - 3.6)
- Sensation imp: 66 (90%)
- Vision imp: 39 (63%)

Image courtesy of Farheen Ali.
Terzis et al. *Plast Reconstr Surg*, 2009.

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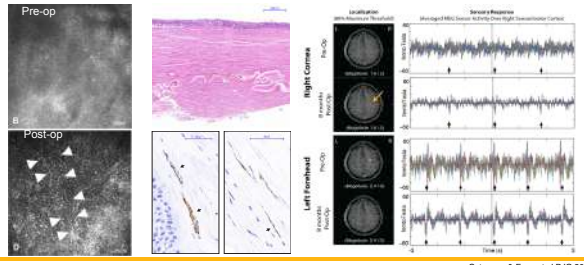
Long term results of ICN



Catapano & Fung et al BJO 2019
Fung et al. *Cornea* 2018

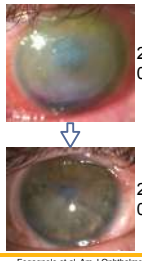
Potential effects of neurotization

- DCN
  - Alopecia
  - Frontal nerve damage
  - Sensory denervation
  - Subgaleal hematoma
  - Subconjunctival neuroma
- ICN
  - Sensory denervation
  - Allodynia
  - Subcutaneous hematoma
- Visual rehabilitation
  - Catapano et al 2019
    - 2 PKP; 2 DALK
    - 3 epithelialized spontaneously

Giannaccare et al. *Cornea*, 2021.
Catapano et al. *Br J Ophthalmol*, 2019.

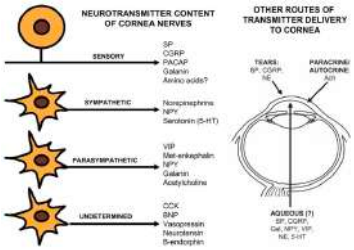
Unanswered questions on neurotization

- Autografts v allografts
  - No comparative studies to date
- Timing of intervention
  - Early prevention of progression v last resort
- Biomarker of efficacy
  - Sensation as primary outcome?



Fogagnolo et al. Am J Ophthalmol, 2020.
Giannaccare et al. *Cornea*, 2021.

Emerging therapies for NK

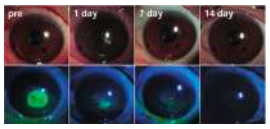


Müller et al. *Exp Eye Res*, 2003.

Substance P (SP)

- Brown et al 1997
  - SP + insulin-like growth factor 1 (IGF-1) in 16mo
  - Complete healing after 1 month

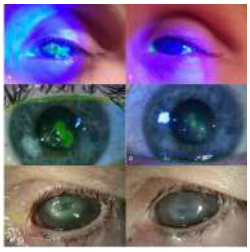
- Nishida et al 2007
  - Used SP-derive tetrapeptide & IGF1
  - Complete healing by D28 in 8/11 patients



Brown et al. *Arch Ophthalmol*, 1997.
Nishida et al. *Jan J Ophthalmol*, 2007

Emerging therapies for NK

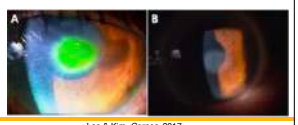
- Insulin
  - Wang et al. 2017: 6/6 healed
  - Soares et al. 2021: 19/21 healed



Wang et al. *Cornea*, 2017.
Soares et al. *Cornea*, 2021.

Emerging therapies for NK

- Insulin
- NGF mimetics
  - Nicergoline
    - Lee & Kim 2015: N=23, 85% healing and improved sensation
    - Miguel-Escuder et al. 2021: N=14, 71% healing
  - Varenicline (NCT04957758)
  - Udonitrectag (NCT04276558)



Lee & Kim. *Cornea*, 2017.
Miguel-Escuder et al. *Ocul. Immunol. Inflamm.*, 2021.

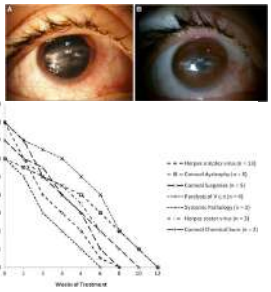
Emerging therapies for NK

- Insulin
- NGF mimetics
- Thymosin ß4
  - Dunn et al. 2010
  - NCT02600429 - results pending

Dunn et al. *Ann. N.Y. Acad. Sci.*, 2010.

Emerging therapies for NK

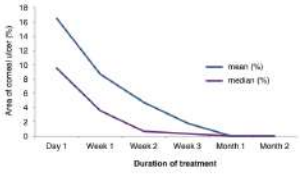
- Insulin
- NGF mimetics
- Thymosin ß4
- PRGF
  - Sanchez-Avila et al. 2018
  - Plasma rich in growth factors (PRGF)
  - Strict pharmaceutical development
  - contain trophic factors, anti-inflammatory, and antibacterial agents
  - NCT02707120 (pending)



Sanchez-Avila et al. *Int. Ophthalmol.*, 2018.

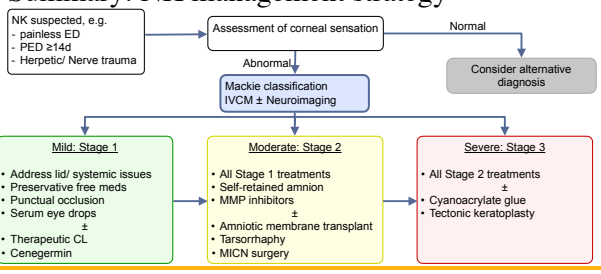
Emerging therapies for NK

- Insulin
- NGF mimetics
- Thymosin ß4
- PRGF
- Matrix regenerating agent
  - Arvola et al., 2016: 33% healed
  - Cochener et al., 2019: 65% healed
  - Salazar-Quiñones et al., 2020: 82% healed



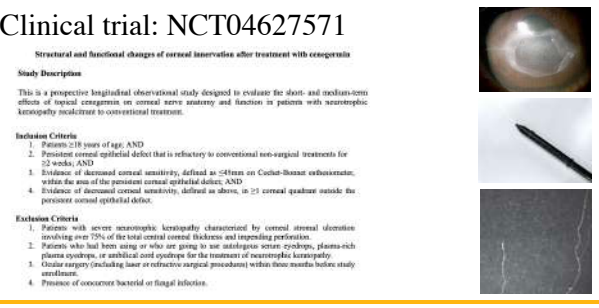
Arvola et al. *Cornea*, 2016.
Cochener et al. *J Fr Ophtalmol*, 2019
Salazar-Quiñones et al. *Arch Soc Esp Oftalmol (Engl Ed)*, 2020

Summary: NK management strategy



Dua et al. *Prog Retin Eye Res*, 2018.
Dana et al. *BMC Ophthalmology*, 2021.

Clinical trial: NCT04627571



Structural and functional changes of corneal innervation after treatment with cenegermin

Study Description

This is a prospective longitudinal observational study designed to evaluate the short- and medium-term effects of topical cenegermin on corneal nerve anatomy and function in patients with neurotrophic keratopathy recalcitrant to conventional treatment.

Inclusion Criteria

1. Patients ≥18 years of age; AND
2. Persistent corneal epithelial defect that is refractory to conventional non-surgical treatments for ≥2 weeks; AND
3. Evidence of decreased corneal sensitivity, defined as ≤45mm on Cochet-Bonnet esthesiometer, within the area of the persistent corneal epithelial defect; AND
4. Evidence of decreased corneal sensitivity, defined as above, in ≥1 corneal quadrant outside the persistent corneal epithelial defect.

Exclusion Criteria

1. Patients with severe neurotrophic keratopathy characterized by corneal stromal ulceration involving over 75% of the total central corneal thickness and impending perforation.
2. Patients who had been using or who are going to use autologous serum eyedrops, plasma-rich plasma eyedrops, or umbilical cord eyedrops for the treatment of neurotrophic keratopathy.
3. Ocular surgery (including laser or refractive surgical procedures) within three months before study enrollment.
4. Presence of concurrent bacterial or fungal infection.

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