Neurotrophic Keratitis: Past, Present, and Future Treatment Options

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- AbbVie
- BioTissue
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- Bausch+Lomb
- Zeiss

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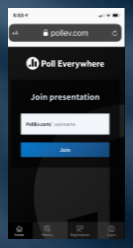

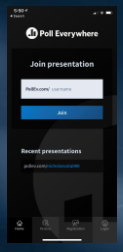

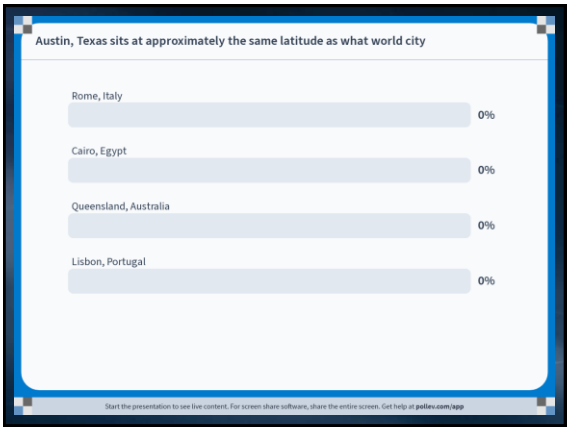

Introduction

- Neurotropic keratopathy is one of the most refractory corneal disorders
- It was first recognized in 1824 by Magendie and Middlemore in 1835
- NK is caused by damage to the trigeminal nerve and the consequent loss of corneal sensation
- It leads to various types of corneal disorders:
  - superficial keratopathy, persistent epithelial defects and corneal ulcers
- The clinical diagnosis of NK is one of the most difficult and challenging corneal diseases to diagnose and manage
  - NK often goes undiagnosed, or misdiagnosed (DED, HSK)
  - However new guidelines and Novel medical and surgical therapies, including the topical administration of nerve growth factor and neurotization and new experimental treatments are now available

Introduction

- New Definition
- *"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 the health and integrity of the tear film, epithelium and stroma"*

Prog Retin Eye Res. 2018 Sep;66:107-131. doi: 10.1016/j.preteyeres.2018.04.003. Epub 2018 Apr 23. ***Neurotrophic keratopathy.*** *Dua HS, Said DG, Messmer EM, et al*

- This implies that NK is the likely diagnosis in the presence of an epithelial defect that does not heal, or heals and breaks down repeatedly in the presence of reduced or altered corneal nerves

How many active patients with NK do you have in your practice?

0-1
2-4
5-7
8-10
>10

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Incidence and Prevalence

- NK has been classified as a rare/orphan disease
  - There are more than 7000 orphan diseases (NIH)
    - Affect more than 30 million Americans
    - 599 approved orphan drugs and more than 400 orphan-designated drugs in clinical trials
      - More than 60% of orphan drugs were biologics
- Prevalence: <1.6/10,000
  - New study suggests higher prevalence: 11/10,000
    - *Saad S, et al. Ocul Surf. 2020;18(2):231-236.*
- NK affects fewer than 65,000 people in US each year
  - Approximately 700,000 worldwide
    - However, NK remains an under-diagnosed condition
- But the global market for NK is expected to increase 5.2% between 2019-2027
  - ~70,000 in US
  - ~735,000 worldwide
- According to Research and Market's report, the global market of neurotrophic keratitis was about $191 million (USD) in 2022 and potentially will increase to $439 million (USD) in 2027

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What is the leading cause of neurotrophic keratitis?

Neurosurgical intervention for trigeminal neuralgia
Herpetic keratitis
Chemical burn
CL wear
Long-term use of glaucoma drops

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Common causes

- The most common condition associated with NK
  - Herpetic keratitis
    - NK develops in an average of 6% of herpetic simplex keratitis cases
    - NK develops in an average of 12.8% of herpes zoster keratitis cases

After herpetic keratitis, the 2nd most common cause of NK is?

Chemical Burns
Neurosurgical intervention to treat Trigeminal Neuralgia
Drug toxicity (timolol, betaxolol, diclofenac sodium, sulfacetamide)
LASIK and PRK
Collagen Cross Linking for Keratoconus
Contact lens wear

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Common causes

- The second most common condition associated with NK:
  - Neurosurgical intervention to treat trigeminal neuralgia
    - NK develops in an average of 2.8%

Etiology of Neurotrophic Keratopathy

- Causes
  - Less common
    - Chemical burns
    - Diabetes
    - Contact lens wear
    - Space occupying lesions
    - Multiple sclerosis
    - Leprosy
    - Long-term topical medication use
    - Chronic ocular surface disease
- Although dry eyes are a feature of NK, DED and NK are different clinical entities
  - However, some convergence is seen in LVC

Etiology of Neurotrophic Keratopathy

- Additional ocular causes
  - Other infections e.g acanthamoeba with nerve damage related to keratoneuritis
  - Abuse of topical anesthetics
  - Drug toxicity (timolol, betaxolol, diclofenac sodium, sulfacetamide 30%)
  - Chronic ocular surface injury or inflammation
  - Corneal dystrophies (lattice, granular)
  - Ocular surgery
    - Alterations of cornea sensitivity have been observed after cataract surgery even if no frank NK has been reported.
    - Penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK) can cause some degree of corneal denervation. up to 12 months after surgery, but NK is not very frequent after this kind of surgery. (Lin et al., 2014)
    - Collagen crosslinking for keratoconus. Treated corneas frequently show a transient reduction of corneal sensitivity (Wasilewski et al., 2013)
    - Development or worsening of NK has been frequently associated with vitrectomy for retinal detachment and photocoagulation to treat diabetic retinopathy (Banerjee et al., 2014)
    - Postsurgical or laser treatment (trauma of ciliary nerves) Routine, single session, indirect laser for proliferative diabetic retinopathy has also been reported as a possible cause of NK. (Tinley and Gray, 2009)

The cause of NK is broad and varied. Which ocular surgery results in the most severe NK?

Corneal Refractive Surgery	A
Collagen Corneal Cross Linking	B
Cataract Surgery	C
Penetrating Keratoplasty	D

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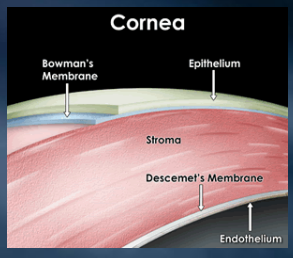
- D. Penetrating Keratoplasty
- All ocular surgery can impact corneal nerve function to some degree (even cataract surgery)
- The more the surgery severs or damages corneal nerves, the greater the risk of NK
- Since a PK results in a full thickness incision through all mid-peripheral corneal nerves, NK is extremely likely

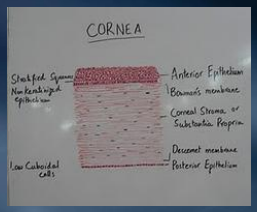
Anatomy



- Corneal Epithelium
  - 5-6 cell layers thick
  - non-keratinized stratified squamous cells
    - No goblet cells
    - Conj epithelium consists of stratified columnar epi w numerous goblet cells
  - Rapidly renewing tissue which loses its surface cells into tear film
  - Turnover 4-6 days
  - Maintains smoothness of optical surface
  - Barrier against micro-organisms
  - Maintains deturgence of stroma
  - Regulates metabolic activity of stromal keratocytes

- The epithelium produces and releases neurotrophic factors to support nerve trophism and healing
- Corneal nerves produce trophic neuromediators for the survival and healing of the epithelium

Anatomy



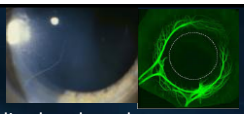
- Corneal Stroma
  - Makes up 90% of corneal tissue
    - Collagen constitutes 80%
  - Composed of 300-500 orthogonally oriented, highly aligned collagen lamellae of uniform size and regular interfibril spacing
    - Responsible for the optical transparency

- Keratocytes are pluripotential cells of neuroectodermal origin
  - prim resp is maintenance and regeneration of stroma
- Capable of wide variety of fibroblastic activity,
  - Phagocytosis of collagen fibrils
  - Secretion of collagen
  - Glycosaminoglycan ground substance
  - Collagenase (MMP) and collagenase inhibitors
- Metabolic function of keratocytes regulated from cytokines from epithelium and other keratocytes
- Keratocyte synthesis of collagen requires ascorbate from the aqueous
- Keratocytes release neuropeptides , neurotrophins and growth factors that influence nerve fiber survival, differentiation and maturation, including NGF

Anatomy

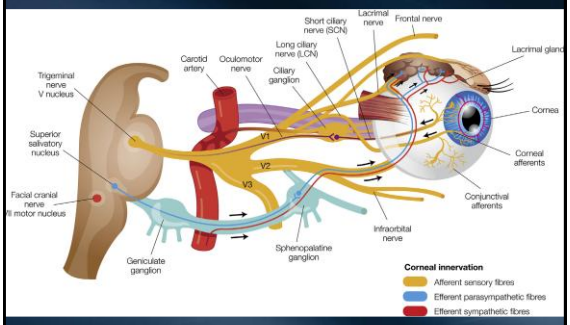
- Cornea is arguably the most sensitive structure in the human body
- The ophthalmic division of the trigeminal nerve (CN V) is responsible for supplying the corneal sensory fibers
  - 200-450 Neurons or 1.5% of the fibers exiting the trigeminal ganglion supply the cornea
  - Each neuron can support hundreds to thousands of nerve endings
  - making it the most sensitive structure in the body (20,000 nerves)
    - Approximately 7,000 nerve endings per square millimeter
- CN V starts in the brainstem and travels through the cavernous sinus into the orbit through superior oblique fissure
- Ophthalmic nerve then divides into Nasociliary, Frontal and Lacrimal nerve
  - the nasociliary nerves (long and short) carry "sensory" supply to the ocular surface via the long ciliary nerves

Anatomy



- Corneal nerves lose their myelin sheath as they enter through the limbus into the anterior third of the stroma where they start grouping into radial nerve bundles
- The nerve fibers then penetrate Bowman's layer and form the sub-basal nerve plexus just below the epithelium before branching out into a more superficial network
- The sub-basal plexus has a mixture of sensory and autonomic fibers
  - carrying trophic supply to the epithelial cells, providing tight control over epithelial turnover at the limbus

Anatomy



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Physiology

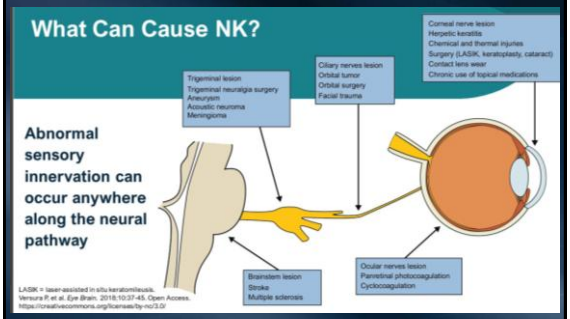
- The physiology of corneal nerves is complex
- NGF is a constitutive molecule present and produced in normal human corneas and important for the development and maintenance of peripheral sensory neurons
  - NGF is essential for the health, survival, growth, and differentiation of sensory and sympathetic neurons
  - It induces the sprouting of neurites in neural cells and restores the function of injured neurons
- Several different functional types of ocular sensory nociceptors neurons exist in the cornea
  - Chemical - polymodal nociceptor neurons
  - Mechanical - selective mechano-nociceptor neurons
  - Thermal - cold thermoreceptor neurons

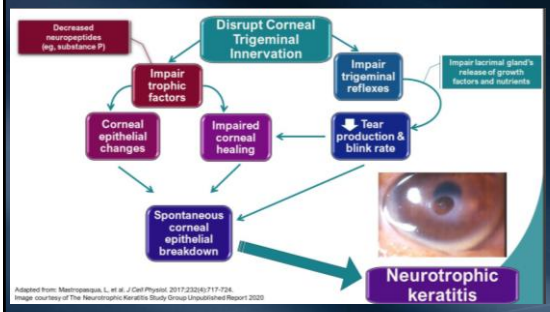
Physiology

- Trigeminal innervation provides trophic supply to the corneal cells by releasing neuromediators and growth factors such as:
  - Substance P, Calcitonin gene-related peptide, acetylcholine and neuropeptide Y
  - These mediators play a key role in the maintenance of corneal tissue integrity and renewal
  - A cross talk between nerves and epithelial cells leads to the release of growth factors such as NGF, brain-derived neurotrophic factor, neurotrophin-3 and 4/5, and glial cell line-derived neurotrophic factor from corneal epithelial cells, as well as keratocytes,
    - All to stimulate nerve growth and survival

Physiology

- In a healthy eye, bidirectional communication between nerves and the immune system forms a negative feedback loop that keeps both systems in check
- Minor insults to the ocular surface are rapidly healed within a continuous trophic environment maintained by corneal innervation and the tear film
- Any persistent alteration of the corneal sensory innervation interfering with the function of the post-ganglionic fibers can lead to NK





Diagnostic Assessment

- Diagnosis of NK is based on the clinical interpretation of the history, general examination of the patient, slit lamp examination of the eye and findings of diagnostic tests
- Clinical examination and tests are directed towards features of NK and of any possible underlying conditions
- A complete and thorough ocular assessment should be performed and not restricted to the cornea or ocular surface

Case History

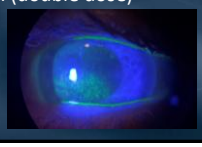
- The diagnosis of NK is a multistep procedure that starts with detection of clinical history conditions associated with trigeminal impairment
- Evaluate medical history and risk factors:
  - Herpetic infections
  - Corneal surgeries
  - Neurosurgical procedures
  - Trauma
  - Systemic diseases (MS, Diabetes)
  - Topical anesthetics
  - Contact lens use

Ophthalmic Examination

- Fluorescein and Lissamine green dyes are useful in assessing subtle changes in the epithelium (mild NK) and frank epithelial defects (moderate and severe NK)
- Tear assessment is important
  - Schirmer's, FL and Lissamine are useful in assessing 'dry eye' signs such as tear meniscus height, tear breakup time and punctate corneal and conjunctival erosions
    - Tear film osmolarity's role in NK is not clear
- Ocular fundus examination may reveal diabetic retinopathy, optic nerve pallor (multiple sclerosis) or swelling from an intracranial neoplasm

Case

- An 80-year-old patient has a history of glaucoma and is on topical hypotensive medications (Combigan BID OU, Azopt BID OU, latanoprost QHS OU). She has 3+ punctate epithelial erosions and presents with a complaint of blurred vision. Denies irritation or discomfort.
- IOP: 13/14
- Gets monthly Eylea injection (double dose)
- Cornea:



- What is the next step?

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What is the next step?

- Discontinue all medications and start preservative-free options
- Add artificial tears
- Test corneal sensitivity
- In-office amniotic membrane

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In the past year, how many times have you tested corneal sensitivity on a patient (for any reason)?

- 0
- 1-2
- 3-4
- 5-10
- >10

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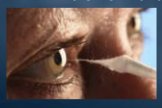
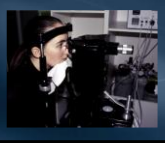
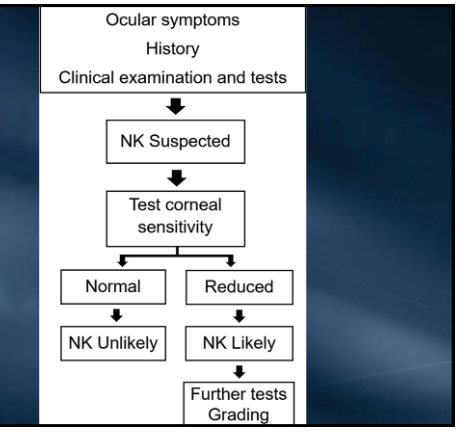
Corneal Sensation

- Assessment of corneal sensation is fundamental to the diagnosis of NK
  - Corneal sensitivity is a commonly missed step, which is a contributing factor to the underdiagnosis and misdiagnosis of NK
  - Should routinely be testing on any pt with H/O HSK, HZO
- NK patients typically show reduced blinking/ sensation to the stimulus
  - if it is normal then NK is unlikely







Corneal Sensitivity

- Corneal sensitivity is not uniform in all corneal areas
  - Most sensitive at apex
  - Least sensitive superiorly and closer to limbus
- Corneal sensitivity varies during the day
  - Lowest sensitivity in the AM
  - Highest sensitivity in PM
- Corneal sensitivity varies with eye color
  - Blue-eyed people are twice as sensitive as brown eyed Caucasians
    - Four times as sensitive as brown eyed African Americans
- Corneal sensitivity decreases with advancing age
  - Especially in 5th decade

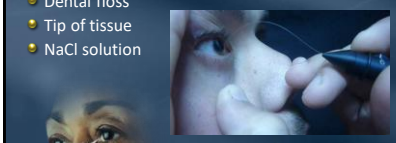
Corneal Sensitivity

- Several methods exist to determine corneal sensitivity, which stimulate various types of nociceptors on the ocular surface
  - Mechanical
  - Chemical
  - Thermal
- The Cochet-Bonnet instrument uses mechanical stimulation and continues to be considered the gold standard in ocular surface sensitivity measurement and is commonly used in clinical practice and in research
- Quantitative measure (Cochet-Bonnet & non-contact)
- Qualitative measure (Cotton wisp and dental floss)

Corneal Sensitivity Testing

Qualitative

- Cotton swab
- Cotton wisp
- Dental floss
- Tip of tissue
- NaCl solution

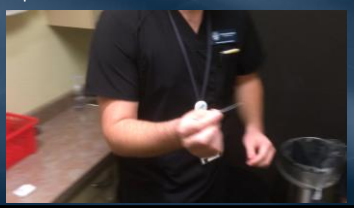


Quantitative

- Cochet-Bonnet Esthesiometer
- Corneal Esthesiometer Brill

Diagnosis

- Corneal sensitivity testing
- Waxed dental floss test
  - Poor man's esthesiometer
  - Unravel 3-4mm and compare both eyes
  - Test 4 quadrants and center



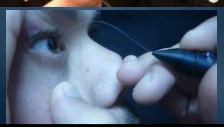
Corneal Sensitivity Tests

- Muro-128 drops
  - *Mandahl A. Hypertonic saline test for ophthalmic nerve impairment. Acta Ophthalmol (Copenh). 1993 Aug;71(4):556-9. doi: 10.1111/j.1755-3768.1993.tb04636.x. PMID: 8249592.*
  - Compared 3% hypertonic saline to cotton wisp and esthesiometer in patients with unilateral acoustic neuromas
    - found to reveal reduced ocular surface sensitivity on the neuroma side in 50% (hypertonic saline), 23% (esthesiometer) and 14% (cotton wool wisp) of cases

Diagnosis

Diagnosis

- Corneal sensitivity testing
  - Corneal Esthesiometry
    - **Cochet-Bonnet esthesiometer**



Using handheld esthesiometer:
1.Extend the filament to full length of 6 cm (60mm)

2.Retract the filament incrementally in 0.5 cm steps until the patient can feel its contact

3.Record the length (NOTE: The shorter the length indicates decreased sensation.)

4.Compare the fellow cornea

5.Repeat steps 1-4 in each quadrant: superior, temporal, inferior, nasal

Diagnosis

- Corneal Esthesiometer Brill
  - Portable, non-invasive
  - Five levels of stimulation
  - Electronic position system
  - Designed to be used in 2 modes: placed on a slit lamp and hand-held
  - Incudes battery and charging dock

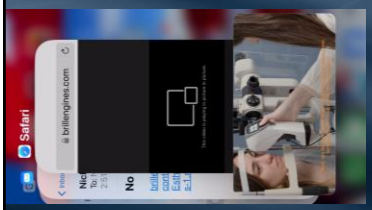
Diagnosis

- Produce pulses of air at different intensities
  - different ranges of pressure, directed at different areas of the surface of the patient's cornea
  - the patient's verbal responses indicate at what pressure range they feel the pulse of air
- Five stimulation levels with a pressure range of approximately 1-2 mbar - 8-9 mbar
  - levels 2 and 3 = a healthy cornea
  - higher levels suggests an alteration in the cornea

Diagnosis

- Brill esthesiometer

First portable, non-invasive, accurate and precise esthesiometer



CEB is an electromedical device for corneal sensitivity assessment through controlled air pulses as stimuli.
It is the first non-invasive and portable corneal esthesiometer.

Clinical Presentation

- Due to epithelial changes and tear film instability, patients will present in the early stage of the disease with symptoms of:
  - Dryness
  - Photophobia
  - Foreign body sensation
  - Inability to read for prolonged periods
  - Impaired quality of vision and reduced blink
- Symptoms are usually worse in the morning or in the presence of aggravating factors such as air conditioning, air travel, draught of hot air from car heating or prolonged use of some computers
  - draught of hot air from computer fans and reduced blinking associated with mental concentration

Clinical Presentation

- Paradoxically, with worsening or severe disease, the symptoms of pain and discomfort may be less or absent due to sensory dullness related to hypoaesthesia or anesthesia of the cornea
- Symptoms in moderate to late stage of NK:
  - Visual impairment appear when central cornea involved
  - Pain and discomfort are less

Classification

- Traditionally NK has been classified into 3 stages as described by Mackie (1995)
  - *Mackie, I.A., 1995. Neuroparalytic keratitis. In: Fraunfelder, F.T., Roy, F.H., Grove, J., Current Ocular Therapy, 4 ed. W. B. Saunders, Philadelphia, pp. 452–454*
- Although the Mackie classification has been in vogue for a number of years, Dua (2018) made some modifications
  - more clinically relevant and indicates the severity and prognosis
    - *Dua HS, Said DG, Messmer EM, et al , Prog Retin Eye Res. 2018 Sep;66:107-131. . Neurotrophic keratopathy.2018.04.003. Epub 2018 Apr 23*
- With incorporation of IVCM and AS-OCT, Mastropasqua / Dua (2019)
  - Considers the severity of subbasal nerve fibers damage and the extension in depth of stromal ulceration
    - *J Cell Physiol. 2019 May;234(5):6108-6115. In vivo microscopic and optical coherence tomography classification of neurotrophic keratopathy. Mastropasqua L1, Nubile M1, Lanzini M1, Calienno R1, Dua HS2*

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Which NK Clinical sign is not an early clinical finding

- Epithelial hyperplasia leading to cloudy epithelium
- Persistent corneal epithelial defect
- Punctate epithelial keratopathy
- Corneal neovascularization
- None of the above

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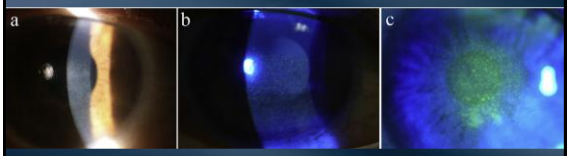
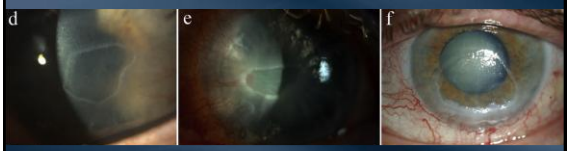
New Classification

- Mild (Stage 1)
  - Epithelial changes only without epithelial defect
  - Epithelial irregularity without frank epithelial defect; tear film instability and symptoms with reduced or absent sensations in one or more quadrants of the cornea
    - Stromal scarring and corneal neovascularization



New Classification

- Moderate (Stage 2)
  - Epithelial defect without stromal defect
  - Frank persistent epithelial defect and corneal hypo-aesthesia/anesthesia
    - Paracentral cornea, typically oval in shape



New Classification

- Severe (Stage 3)
  - Stromal involvement
  - Stromal corneal ulcer, stromal edema, stromal infiltrates, stromal thinning due to melt, and perforation

Treatment and Management

- Left untreated, NK can evolve into a devastating condition culminating in anatomical loss of the eye
  - Loss of vision is common even with treatment
- The objective of treatment is to arrest progression and reverse NK changes that have occurred at the time of presentation
  - Treatments limited to addressing symptoms
  - Epithelial healing
  - Prevent progression of corneal damage
  - Caution with topical medications

Treatment and Management

- Mild NK
  - Evaluation of side effects of systemic therapies such as neuroleptic, antipsychotic, and antihistamine drugs
  - Treat concurrent ocular surface problems, especially infection of ocular surface/ lacrimal passage
  - Anti-inflammatory therapy if inflammation present (non-steroidal anti-inflammatory drugs can be toxic)
  - Tear substitution/administration of topical preservative-free lubricants
  - Punctal occlusion
  - Correction of lid abnormalities
  - Debridement of sick epithelium
  - Recombinant Human (rh)NGF (cenegermin/Oxervate)

Treatment and Management

- Moderate NK
  - Prophylactic topical preservative-free antibiotics
  - Prevention of melting with Citrate/tetracycline/macrolides (if stromal involvement is threatened)
  - Recombinant Human (rh)NGF (cenegermin/Oxervate)
  - Q10 co-enzyme
  - Cacicol 20/RGTA
  - Serum eye drops, platelet-rich plasma
  - Corneal or scleral therapeutic contact lenses
  - Non-surgical eyelid closure
  - Debridement of 'rolled' edges of epithelial defect
  - Tarsorrhaphy
  - Amniotic membrane transplantation usually single layer as patch
  - Conjunctival flaps

Treatment and Management

- Severe NK
  - rhNGF and RGTA are likely to be of particular help
  - Amniotic membrane, multilayer, usually as graft
    - Can be combined with tarsorrhaphy
  - Corneal grafts (tectonic, lamellar or full thickness)

In the event of perforation

- Cyanoacrylate tissue adhesive with therapeutic contact lens
- Fibrin glue
- Amniotic membrane graft or corneal grafts

Case

- An 80-year-old patient has a history of glaucoma and is on topical preservative-free hypotensive medications and preservative-free artificial tears. She has 3+ punctate epithelial erosions reduced corneal sensation.
- What is the next step?

What would be an appropriate next step?

Topical corticosteroids

Autologous serum drops

Cyclosporin or lifitegrast

Oral doxycycline

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Biological Tear Substitutes

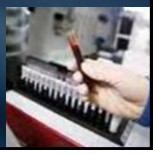
- The use of biological tear substitutes have been reported in numerous studies to help patients with NK and OSD
- These options have the advantage of providing factors that promote corneal and conjunctival epithelial health and homeostasis
- There is evidence that they maintain the morphology and support the proliferation of primary epithelial cells better then pharmaceutical tear substitutes

Autologous Serum

- Use first described in 1984 by Fox et al
  - for keratoconjunctivitis sicca)

Fox RI, Chan R, Michelson J, et al. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. Arthritis Rheum1984;29:577-83.

- Dry Eye Disease
  - DEWS II – Step 3 Tx
- Recurrent Corneal Erosions
- Post-laser epithelial Keratomileusis (LASEK)
- Late onset bleb leaks
- Tissue necrosis after orbital implants
- Neurotrophic Keratopathy



- Utilizes patients own blood serum
- Blood is drawn and serum is spun down and mixed with artificial tears / 0.9% sodium chloride
  - Doesn't contain red blood cells and clot factors
- Replaces individualized antibodies
- Non-preserved, non-antigenic

Autologous Serum

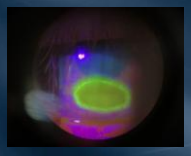
- Contains essential components in tears
  - epidermal growth factor
  - hepatocyte growth factor
  - Fibronectin
  - Albumin
  - neurotrophic growth factor
  - vitamin A
    - inhibits the release of inflammatory cytokines
    - increases the number of goblet cells and mucin expression in the conjunctiva
- Potential complications
  - Immunoglobulin deposits
  - Corneal infiltrates
  - Conjunctivitis
  - Decreased corneal sensitivity

Biologic Tear Substitutes

- Available BTS
  - Autologous Serum
  - Allogeneic Serum
  - Umbilical Cord Serum
  - Fingerprick Autologous Blood
  - E-PRP - Eye Platelet Rich Plasma
  - PRGF – Plasma Rich in Growth Factors
  - Platelet Lysate

Case

- An 80-year-old patient has a history of glaucoma and is on topical preservative-free hypotensive medications and preservative-free artificial tears. She has 3+ punctate epithelial erosions, reduced corneal sensation, and a 2.5 mm x 3 mm central epithelial defect.



- What is the next step?

What could be an appropriate next step?

In-office amniotic membrane

Bandage contact lens

Tarsorrhaphy

Pressure patch

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Amniotic Membrane Therapy

- Thin but tough transparent pair of membranes, which hold a developing embryo (and later fetus) until shortly before birth.
- The primary function of the amniotic membrane is to protect the fetus from injury.
  - 1. Anti-inflammatory
  - 2. Anti-scarring
  - 3. Anti-angiogenic

Amniotic Membrane Therapy

- Amnion is avascular and a translucent membrane composed of an inner layer of epithelial cells which are planted on a basement membrane
- Amnion is made of Collagen I, III, IV, V and VII, laminin and fibronectin of which IV, VII, laminin and fibronectin are also found in conjunctiva and cornea

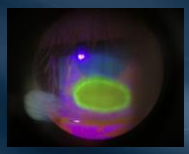
Amniotic Membrane Therapy

- Promotes Epithelialization
- Suppresses Inflammation
- Inhibits Scarring
- Inhibits Angiogenesis
- Neurotrophic Factors
- Anti-Microbial Agent

All without the harmful side effects found in topical and oral medications

Case

- An 80-year-old patient has a history of glaucoma and is on topical preservative-free hypotensive medications and preservative-free artificial tears. She has 3+ punctate epithelial erosions, reduced corneal sensation, and a 2.5 mm x 3 mm central epithelial defect.
- What is the next step?



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What would be an appropriate next step?

- Cenegermin-bkbj
- Bandage contact lens
- Tarsorrhaphy
- Pressure patch

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Oxervate (cenegermin)

- Dompé Pharmaceutical
- First treatment specifically indicated for neurotrophic keratitis
- First ever topical biological medication in the ophthalmic space
- First ever application of a human nerve growth factor as a drug or treatment
- Was authorized in Europe in 2017
- Received Orphan Drug Designation, Fast Track Status, Breakthrough Therapy Designation
  - Ultimately Priority Review

Oxervate

- 151 patients in 2 studies
  - 8 week, randomized controlled
  - Multi-center, double masked
- Drops used 6x/day (Q2H) in affected eye(s) for 8 weeks
  - Compared drops to placebo or different concentration (Study 1)
  - Compared drops to placebo (Study 2)
- Results: Complete corneal healing in 8 weeks in up to 72% of patients (Oxervate) vs. placebo

Oxervate (cenegermin)

- Approved August 2018 (Europe July 2017)
  - Rolled out 1st Quarter 2019 (January 2019)
- The regenerative potential of NGF was discovered by Nobel-prize winning scientists (Rita Levi-Montalcini and Stanley Cohen 1986), but its therapeutic potential was not realized in eyecare until Dompé's research and development center in L'Aquila, Italy, created cenegermin-bkbj
  - a recombinant version of human NGF, through a unique development process

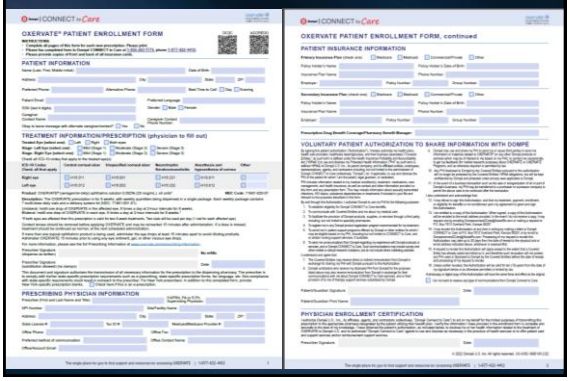
Oxervate

- Oxervate is supplied in a weekly carton containing 7 multiple-dose (glass) vials in an insulated pack in a “Delivery System Kit”
  - Contains 8 vial adapters, 45 pipettes, 45 sterile disinfectant wipes and a dose card
- Within 5 hours of leaving the pharmacy the weekly carton should be refrigerated between 36-46F (up to 14 days)
  - Contact lenses cannot be in during installation (including BCL), limits medication distribution
  - Do not freeze (re-freeze)
  - Do not shake
  - Discard any unused portion after 12 hours

Oxervate

- Side Effects
  - Eye pain (most common - 16%)
  - Less than 10%
    - Corneal deposits
    - Foreign body sensation
    - Ocular hyperemia
    - Ocular inflammation
    - Tearing

Oxervate


OXERVATE* PATIENT ENROLLMENT FORM

PATIENT INFORMATION

TREATMENT INFORMATION/PRESCRIPTION (physician to fill out)

PRESCRIBING PHYSICIAN INFORMATION

OXERVATE PATIENT ENROLLMENT FORM, continued

PATIENT INSURANCE INFORMATION

VOLUNTARY PATIENT AUTHORIZATION TO SHARE INFORMATION WITH DOMPE

PHYSICIAN ENROLLMENT CERTIFICATION

Therapeutic Lenses

- Rigid gas permeable scleral contact lenses are vaulted away from the cornea and supported by the anterior sclera
- The design creates a reservoir between the lens and cornea that captures therapeutic substances and increases retention time of therapeutic agents and lubricants on the ocular surface
  - The prosthetic replacement of the ocular surface ecosystem (PROSE)
- The use of contact lenses in the context of NK must be accompanied by extreme vigilance
  - The reduction of sensation reduces ‘alarm’ signals for infection
  - If used, prophylactic use of topical non-preserved antibiotics is advised

Oral Ascorbate

- Vitamin C is an important modulator of collagen production, acting as a cofactor for the hydroxylation of proline and lysine residues in procollagen
- It enhances the production of several types of collagen in stromal keratocytes
- Dose
  - 1000mg tab BID-TID
    - Oral administration of 2.0 g of vitamin C was found to saturate the aqueous humor, with further vitamin C supplementation having no effect on its concentration in aqueous humor

Efficacy of Systemic Vitamin C Supplementation in Reducing Corneal Opacity Resulting from Infectious Keratitis. Yong-Wun Cho, MD, Woong-Sun Yoo, MD, Seong-Jae Kim, MD, et al. Medicine • Volume 93, Number 23, November 2014

Corneal Neurotization

- Corneal neurotization is a revolutionary surgical procedure in which a donor nerve graft is coapted to the damaged nerve
- The technique relies on a transfer of a healthy nerve segment to the corneo-limbal area, to reestablish a basis for sub-basal plexus regeneration, and hence reversal of the neurotrophic disease
- Corneal reinnervation can be performed by direct nerve transfers or by nerve graft interpositions

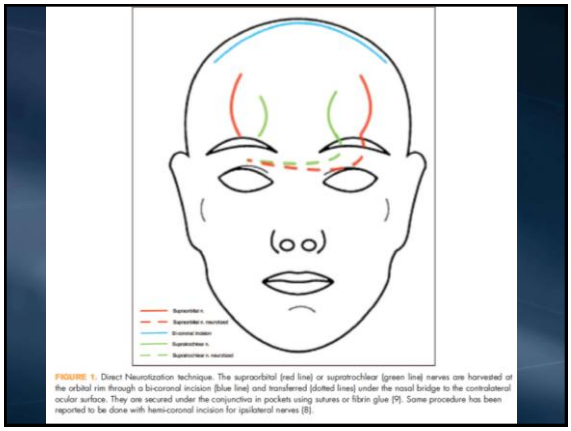


FIGURE 1. Direct Neurotization technique. The supraorbital (red line) or supratrochlear (green line) nerves are harvested at the orbital rim through a bi-coronal incision (blue line) and transferred (dotted lines) under the nasal bridge to the contralateral ocular surface. They are secured under the conjunctiva in pockets using sutures or fibrin glue (9). Some procedure has been reported to be done with hemi-coronal incision for ipsilateral nerves (8).

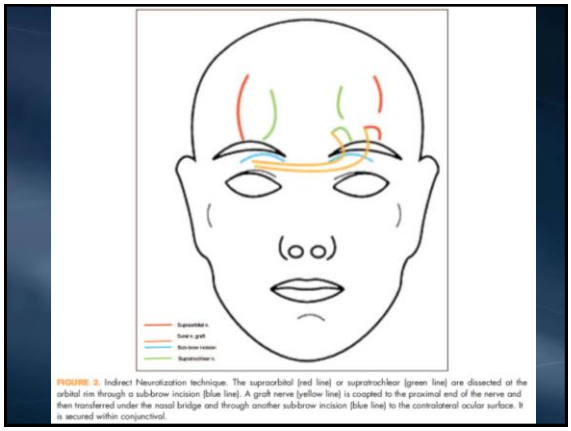


FIGURE 2. Indirect Neurotization technique. The supraorbital (red line) or supratrochlear (green line) are dissected at the orbital rim through a sub-brow incision (blue line). A graft nerve (yellow line) is coapted to the proximal end of the nerve and then transferred under the nasal bridge and through another sub-brow incision (blue line) to the contralateral ocular surface. It is secured within conjunctival.

Future Treatments

Topical Insulin

- A retrospective, observational analysis of eyes with NK in stages 2 and 3 refractory to standard medical and/or surgical treatment which were treated with topical insulin.
  - Topical insulin (1 unit per mL) was applied 4 times a day
    - Therapeutic CL used during treatment
  - Treatment was continued until PED or ulcer resolved and then tapered accordingly
  - The primary outcome of the study was the complete resolution of the PED or ulcer
- Purpose: To evaluate the clinical outcome of patients with refractory Neurotrophic Keratopathy (NK) in stages 2 and 3 treated with topical insulin.

Topical Insulin

- 21 eyes included in the observational study
  - 90% achieved complete re-epithelialization of the PED and/or persistent ulcer within 7 to 45 days of follow-up
    - mean number of days until complete re-epithelialization was significantly lower in NK stage 2 (18 ± 9 days) when compared with NK stage 3 (29 ± 11 days)
    - The best-corrected visual acuity improved significantly in both Stage 2 and Stage 3 patients

- Soares RJDSM, Arêde C, Sousa Neves F, da Silva Fernandes J, Cunha Ferreira C, Sequeira J. Topical Insulin-Utility and Results in Refractory Neurotrophic Keratopathy in Stages 2 and 3. Cornea. 2022 Aug 1;41(8):990-994. doi: 10.1097/ICO.0000000000002858. Epub 2021 Sep 3. PMID: 34483270.

Topical Insulin

- Small (6) case series of patients with neurotrophic ulcers refractory to other therapies
  - 1 unit per milliliter of artificial tears with propylene glycol and polyethylene glycol base
  - Used 2-3x/day for up to 1 month
- MOA speculates restoration of corneal nerves and/or improved epithelial cell migration
- Insulin-like growth factor-1 (IGF-1) has been shown to be an important modulator of corneal wound healing
  - IGF-1 was shown to act synergistically with substance-P to promote corneal epithelium wound healing

- Wang AL, Weinlander E, Metcalf BM, Barney NP, Gamm DM, Nehls SM, Struck MC. Use of Topical Insulin to Treat Refractory Neurotrophic Corneal Ulcers. Cornea. 2017 Nov;36(11):1426-1428. doi: 10.1097/ICO.0000000000001297. PMID: 28742619; PMCID: PMC5633504.

Tyrvaya (varenicline nasal spray)

- Phase 2, multicenter, randomized, controlled, double-masked study designed to evaluate the safety and efficacy of varenicline nasal spray in subjects with Stage 1 NK
- Diagnosis of Stage 1 NK as defined by the Mackie Criteria and meeting all other study eligibility criteria will be randomized 1:1
  - varenicline nasal spray 1.2 mg/ml or placebo nasal spray for 8 weeks three times daily
- 113 enrolled, 103 completed
- Just completed May 2024

Tyrvaya (varenicline nasal spray)

- Primary Outcome Measures
  - Mean change from baseline in corneal fluorescein staining at Week 8
- Secondary Outcome Measures
  - Mean change from baseline in visual acuity at Week 8
  - Data not published yet

Thymosin Beta 4 (Tβ4)

- ReGenTree
- A Phase 3, Multi-Center, Randomized, Parallel, Double Masked, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of RGN-259 Ophthalmic Solution (0.1% Thymosin beta) for the treatment of Neurotrophic Keratopathy
  - Currently recruiting for Stage 2 or Stage 3 NK
  - Documented proof of reduced corneal sensitivity (C-B)
  - 4 weeks of treatment, 5x/day

Thymosin Beta 4 (Tβ4)

- Formulated as preservative-free eye drops for the treatment of both dry eye syndrome and neurotrophic
- Synthetic copy of the naturally-occurring 43-amino acid peptide that is found in all tissues and in all nucleated cells

BRM424

- BRIM Biotechnology
- Pre-clinical studies demonstrate that BRM424 stimulates the proliferation and differentiation of corneal limbal stem cells
  - This direct activation of limbal stem cells can lead to fast and effective corneal healing
- BRM424 received its Orphan Drug Designation (ODD) for NK from the US FDA in 2022
- Phase 2 trial of BRM424 was initiated in Q2, 2023

CSB-001 0.1%

- Claris Bio
- Human recombinant dHGF (5-amino acid deleted hepatocyte growth factor)
- Multi-Center, Randomized, Double-asked, Vehicle-Controlled, Parallel-Group, Study to Evaluate the Safety and Efficacy of CSB-001 Ophthalmic Solution 0.1% in Stage 2 and 3 Neurotrophic Keratitis Subjects
- Primary Outcome: Proportion of subjects achieving complete corneal healing as assessed by the Central Reading Center

CSB-001 0.1%

- 5 amino acid deleted - hepatocyte growth factor (HGF)
- Paracrine growth factor, secreted by mesenchymal cells
- A single receptor – c-MET, present in cornea

- Therapeutic benefits of dHGF are well suited to NK
  - Epitheliotrophic – Accelerates healing
  - Anti-fibrotic – Reduced scarring Improves vision outcomes
  - Neurotrophic – Promotes corneal nerve regeneration
  - Anti-inflammatory – Reduces nerve damage
- Topical HGF reduces inflammation and promotes "ordered" wound healing

Emerging Treatments

- NGF Mimetics
  - synthetic molecule meant to mimic nerve growth factor
  - designed to bind NGF receptors with a high affinity and may be less costly than recombinant NGF
  - Nicergoline
    - drug used to treat dementia, especially in cases with vascular etiologies, is an NGF drop in development

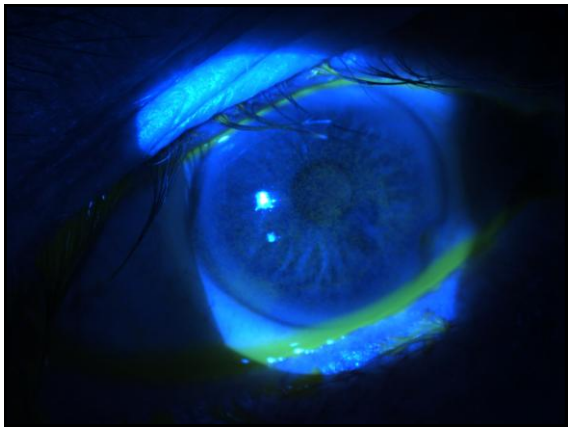
Case Study

Case Report

- 61 yo WM Scott C
- C/O blurred vision, both distance and near for past couple of weeks. No pain or discomfort. Was given allergy drop but no help
- H/O Lung, Liver, Esophageal and Kidney Cancer
  - Has had Nephrecotmy, Esophageal surgery, had radiation to neck area and on Chemo (Tretinoin) 10mg oral
- Entering VA
  - OD -6.75 -2.50 x 028 20/70+
  - OS -6.00 -1.00 x 151 20/150
  - OU 20/40-
- PERRLA, EOM's CVF WNL

Case Report

- DEQ5 = 4
- Tear lab
  - OD 310
  - OS 297
- InflammaDry
  - OD Positive
  - OS Positive
- SLE
  - 3+ diffuse FL stain OU

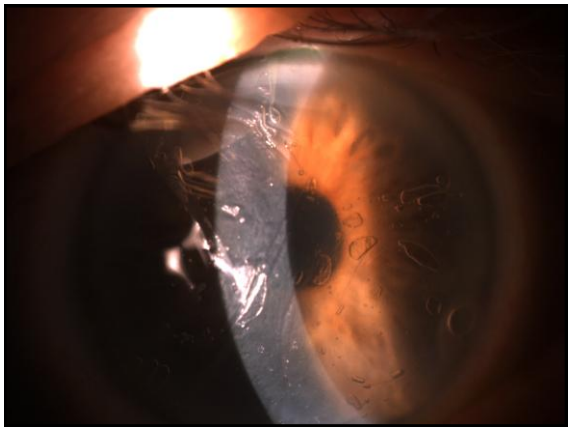


Case Report

- History
  - Significant for medications and treatments that can reduce function of the Trigeminal nerve
- Symptoms
  - Main complaint is blurred vision
  - No complaining of pain despite involved cornea
- Diagnostic Testing
  - Vital dyes show epithelial disruption that is not improving with conventional treatments
- What test that should be performed
- Cochet-Bonnet Corneal sensitivity score reduced
  - 35mm / 11.5 mg/S OD, OS (normal 52.5mm)

Case Report

- Diagnosis
  - Mild / Stage 1 Neurotrophic Keratopathy OU
- Plan
  - Copious non-preserved artificial tears q1-2h
  - Apply dehydrated amniotic membrane with BSCL
  - Initiate Restasis BID OU – once BSCL removed
  - Recommended 8-week course of Oxervate
    - Initiated paperwork



Case Report

- RTO 1 week after Tx reporting much improved
  - Entering VA OD 20/40, OS 20/25
- Cornea 1+ punctate erosions
- Plan CPM, Oxervate was approved
- QOL improved for last few months

Case Report

Case Presentation

- BR, 62 year-old Caucasian male
- Initially seen May 2019
  - Sent by his PCP for shingles (right side)
  - Already taking Valtrex 1000 mg TID
  - Reports previous herpetic infections x 25 years
  - Medical and ocular history unremarkable
  - Medications: None
- VA 20/30 OD, 20/20 OS
- Cornea: Faint scarring superior nasal
- Lids: Trichiasis RLL
- Fundus: Normal
- RTO x 1 month

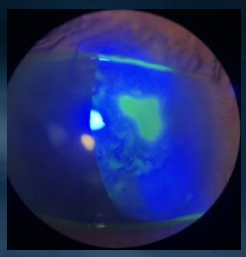
Case Presentation

- Patient returned July 13, 2020
  - c/o irritation right eye
  - VA: 20/30 OD, 20/20 OS
  - Cornea: Dendrite OD
  - Started Zirgan Q3H OD, Valtrex 500 mg TID, RTO x 1 week
    - Initiated a discussion about prophylactic dosing
- July 21, 2020
  - Significant improvement in appearance and comfort
  - Dendrite not fully resolved
  - Continue Zirgan Q3H OD, RTO x 1 week
- August 5, 2020
  - Dendrite resolved, Zirgan TID OD x 1 week then discontinue

Case Presentation

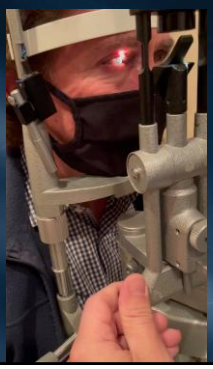
- Patient was seen by outside practitioner August 9, 2021
- c/o pain in the right eye and light sensitivity x 3 days
  - Prescribed Tobradex TID OD x 3 weeks
- Returned August 31, 2021
  - Slight improvement in comfort
  - Cornea: dendrite
  - DC Tobradex, add Zirgan Q3H OD, add Valtrex 500 mg TID
  - RTO x 1 week
- Returned September 13, 2021
  - Better comfort
  - Zirgan TID OD x 1 week, continue Valtrex
  - RTO x 3-4 weeks

Case Presentation

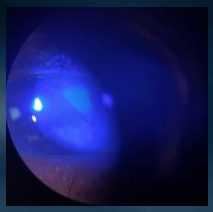


- October 6, 2021
  - Improved comfort
  - BCVA 20/80 OD, 20/25 OS
  - Cornea
    - Neurotrophic ulcer
  - Corneal sensitivity
    - OD: 45 mm
    - OS: 60 mm
  - Diagnosis: Grade 2 NK
  - Plan: Start Oxervate paperwork, ProKera Slim placement OD

Case Presentation

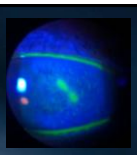


Case Presentation

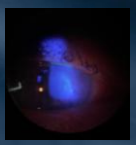


- October 21, 2021
- Defect still present
- Replaced PK Slim
  - X3
- Started Oxervate October 30, 2021 (6x/day- Q2H OD)

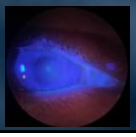
Case Presentation



- November 10, 2021

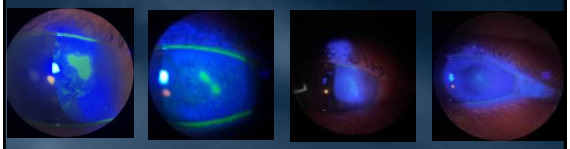


- November 24, 2021



- December 20, 2021

Case Presentation



- 8 week Oxervate course
- BCVA returned to 20/70
- Process of getting fitted with scleral lenses

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What is the most important factor in diagnosing NK?

- A clinical history of conditions associated with Trigeminal impairment
- Presence of corneal epithelial defect or ulcer
- Decreased corneal sensation
- History of use of chronic preserved topical medications

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- C. Decreased Corneal Sensitivity
- Although a history of medical conditions such as DM, HZO or clinical findings of PED or ulcer can be highly suspicious of NK
  - Nothing is more diagnostic than decreased corneal sensitivity
- A test for corneal sensation should be performed on every patient with corneal epitheliopathy or an epithelial defect

When poll is active, respond at **pollev.com/nicholascola090**
Text **NICHOLASCOLA090** to **22333** once to join

Now how many active NK patients do you think you have in your practice?

- 0-1
- 2-4
- 5-7
- 8-10
- >10

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Conclusion

- All eye care providers who treat patients with anterior segment disease must exercise their clinical skills and judgement to screen for and identify patients with NK, which means testing for corneal sensitivity
- We are just beginning to understand the pathophysiology of NK, and how specific treatments can affect the anatomy and physiology of the cornea
- Biologic tear substitutes, oral ascorbate, therapeutic scleral lenses, self retaining amniotic membranes, NGF and corneal neurotization all offer a lot of promise to allow patients with NK a better quality of life

Thank you

Please feel free to contact us:

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