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# **Consensus Panel Highlights:** Updated Approaches to Neurotrophic Keratitis Staging and Treatment

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This continuing education (CE/CME) activity captures content from a virtual panel discussion.

#### **Activity Description**

This supplement summarizes a virtual consensus panel discussion focusing on early diagnosis and treatment of neurotrophic keratitis as well as a review of therapies.

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This certified CE/CME activity is designed for ophthalmologists and optometrists.

#### **Learning Objectives**

Upon completion of this activity, the participant should be able to:

- **Explain** diagnostic strategies for neurotrophic keratitis (NK) and identify patients with stage 1 disease
- **Describe** current and emerging treatment options for stage 1 NK
- **Develop** personalized treatment plans for patients with stage 1 NK
- **Discuss** new data on novel treatments for NK and how it compares to traditional treatments

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1. Please rate your confidence in your ability to develop personalized treatment plans for patients with stage 1 neurotrophic keratitis (NK) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

- A. 1
- B. 2
- C. 3
- D. 4
- E. 5
- 2. All of the following statements about the prevalence of NK are true EXCEPT:
  - A. NK has historically been thought of as an extremely rare disease
  - B. NK has traditionally been diagnosed in stage 2 or stage 3 of the disease
  - C. Stage 1 NK is much more prevalent than has historically been thought
  - D. Stage 1 NK is extremely rare
- 3. A 64-year-old patient with a history of dry eye disease (DED) presents to your clinic for his third follow-up. He has been treated with artificial tears, punctal plugs, and cyclosporine with no significant improvement in exam findings. On exam, you note 2+ staining and epitheliopathy. The patient states that his eyes feel fine. Which of the following is a reasonable next step in management?
  - A. Suspect DED and escalate dry eye therapy
  - B. Suspect herpetic keratitis and initiate antiviral therapy
  - C. Consider NK and test for corneal sensitivity
  - D. Consider blepharoplasty

## 4. All of the following statements regarding corneal sensitivity testing are true EXCEPT:

- A. Cotton wisp testing is a reasonable testing method for corneal sensitivity
- B. Wax dental floss is a reasonable testing method for corneal sensitivity
- C. It is important to test all corneal zones when testing for corneal sensitivity
- D. Testing central corneal sensation is adequate when testing for corneal sensitivity

# 5. You are evaluating a patient with punctate epitheliopathy. Cotton wisp testing reveals decreased corneal sensitivity. All of the following are reasonable treatment options for this patient EXCEPT :

#### A. Punctal occlusion

- B. Amniotic membrane transplant
- C. Autologous serum drops
- D. Topical ketorolac

#### 6. A patient with stage 1 NK presents to your clinic. He continues to progress despite treatment with frequent preservative-free artificial tears and punctal occlusion. All of the following options are reasonable next steps EXCEPT:

- A. Oral steroids
- B. Topical cyclosporine or lifitegrast
- C. Autologous serum drops
- D. Topical steroids

#### 7. What stage NK can cenegermin be used for?

- A. Stage 1
- B. Stage 2
- C. Stage 3
- D. All of the above
- 8. A 42-year-old patient with a history of right-sided acoustic neuroma removal with resulting right-sided facial weakness presents to your office with a 2 mm x 3 mm inferior corneal oval defect with rolled edges. She has been on gentamycin QID, artificial tears QID, and ointment at night for 3 months without significant improvement. All of the following are reasonable treatment options for this patient EXCEPT:
  - A. Consider amniotic membrane transplant
  - B. Consider cenegermin
  - C. Consider tarsorrhaphy
  - D. Continue current regimen
- 9. A 78-year-old patient with a history of cataract surgery and primary open-angle glaucoma presents to your office for evaluation. He had cataract surgery 3 months ago and has been on latanoprost qhs OU for many years. Examination shows inferior corneal staining. Which of the following statements about this patient is TRUE?
  - A. Chronic exposure to benzalkonium chloride (BAK) from this patient's glaucoma drops can lead to gradual NK
  - B. This patient is unlikely to have NK
  - C. Latanoprost drops have a low BAK content and are optimal for patients with NK
  - D. This patient is not a candidate for cenegermin

## 10. Which of the following statements about ocular surface disease (OSD) and NK is TRUE?

- A. OSD is separate from NK with very different exam findings
- B. NK often overlaps with OSD in exam findings, and corneal sensitivity testing can help differentiate the two conditions
- C. OSD presents with epitheliopathy while NK presents with an epithelial defect
- D. OSD and NK are clinically indistinguishable

# 11. A 58-year-old patient with a history of LASIK presents for repeat refractive surgery evaluation. On examination, he has mild inferior staining in both eyes that has not improved with 2 weeks of artificial tear treatment. What is the best next step in management for this patient?

- A. Schedule refractive surgery
- B. Schedule tarsorrhaphy
- C. Full DED workup, lid evaluation, and corneal sensitivity testing
- D. Observation

# **Consensus Panel Highlights:** Updated Approaches to Neurotrophic Keratitis Staging and Treatment

#### **INTRODUCTION**

Neurotrophic keratitis (NK) is a rare, degenerative, and potentially blinding corneal disease caused by damage to the trigeminal nerve and cranial nerve 5, resulting in a progressive loss of corneal sensation<sup>-1,2</sup> Evidence suggests that NK is more prevalent than previously thought and often overlaps with ocular surface disease (OSD).<sup>3</sup> Early diagnosis through corneal sensitivity testing is key to initiate prompt treatment and avoid progression. Our understanding of NK staging is evolving, with a new classification proposed focused on treatment at earlier stages. During the following discussion, faculty discuss best practices in identifying NK, how to incorporate the proposed staging system, and where newly approved and emerging agents fit into the treatment paradigm.

- John A. Hovanesian, MD, Program Chair and Moderator

#### SCREENING FOR AND STAGING NEUROTROPHIC KERATITIS

**Dr. Hovanesian:** How big of a problem is NK? How many patients are affected by it?

**Preeya Gupta, MD:** NK has historically been thought of as an extremely rare disease that was only seen by specialists.<sup>3,4</sup> Part of that is because of how we detect NK. We've only traditionally diagnosed NK once a patient has stage 2 or stage 3 disease, where there's a breakdown of the corneal epithelium and some stromal thinning.<sup>3,5</sup> However, all of these patients started with stage 1 disease, which is a presentation of epitheliopathy but without breakdown of the epithelium such that there's exposure of the stroma. Point being, the prevalence of NK in its earlier form is vastly more prevalent than we've historically seen, which is supported by several large studies.<sup>1</sup>

Walter O. Whitley, OD, MBA, FAAO: We used to think of NK as a rare disease, but now that we're more aware of it. Now that





"For the patient to be neurotrophic, there has to be a reduction or loss of corneal sensation, which can only be determined by testing for corneal sensitivity."

- Victor L. Perez Quinones, MD

we are actually looking for it and testing for it, we're seeing it quite often in our clinics. I graduated right about when cyclosporine for dry eye disease (DED) came out, and we had patients on various dry eye therapies for many years who weren't getting better. They have this constant dry eye presentation of punctate keratopathy that's not resolving. In those situations, we need to rethink our diagnosis and say that this isn't DED, it's something else. Traditionally, when we thought of NK we thought of ulcers and perforations, which is why we considered it so rare.

**Dr. Hovanesian:** How do you go from seeing a patient with OSD to narrowing the diagnosis to NK?

**Victor L. Perez Quinones, MD:** It's about how you make the diagnosis. For the patient to be neurotrophic, there has to be a reduction or loss of corneal sensation, which can only be determined by testing for corneal sensitivity.<sup>3,5</sup>

**Karen P. Skvarna, OD:** Corneal sensitivity testing is quick and easy to do with a cotton wisp. You lightly touch the cornea and see if there's a sensation.

**Dr. Hovanesian:** What I do with a cotton tip is tease the end apart so that I get a very fine wisp rather than using the solid part of it. We only need a few threads of cotton fiber. Are there other ways you test for corneal sensitivity?

**Dr. Gupta:** I like to use wax dental floss that has that fine tip to it. A cotton wisp is fine, too; whichever you have handy. What's

important is testing all corneal zones (central, superior, inferior, temporal, and nasal) in both eyes because patients can have isolated or regional neurotrophism.<sup>3,5</sup> If you only check central sensation, you might miss the diagnosis in some patients. Quantitative measurements of corneal sensitivity can be taken using a Cochet-Bonnet aesthesiometer, whereby the cornea is touched with a nylon filament. But we rarely have access to that in the clinic. It's more research oriented and impractical.

**Dr. Whitley:** I've also used dental floss and a cotton wisp. In addition to testing the various zones, you also need to note if the sensitivity is present, reduced, or absent. Grading the level of sensitivity helps determine next steps.

**Dr. Hovanesian:** Is it reasonable to say that we should test everyone for corneal sensitivity during a routine dry eye workup?

**CONSENSUS POINT #2:** Diagnosing corneal sensitivity is reasonable for patients with 2+ staining, epitheliopathy, and suspected NK symptoms (more signs than symptoms)

**Dr. Gupta:** Yes, I think that is very reasonable. In my clinic when patients come in for a dry eye evaluation and they have anything more than 2+ staining, I check corneal sensation. We know that patients with stage 1 disease have an increasing confluence of punctate epithelial erosions, especially patients who have tried multiple therapies for dry eye that didn't work. It's also important to ask patients how bad they feel their disease is, not from a vision standpoint but from a comfort standpoint because that can also be a big clue. As DED progresses, patients often become neurotrophic as a protective mechanism. We've all seen that dry eye patient early in their disease who reports 10 out of 10 symptoms with a lot of trouble seeing. However, when you examine them, there's no corneal staining. By the old standard, we'd say that patient doesn't have dry eye. But we know from our modern definitions of dry eye that there's a lot going on at the micro level that's creating dysfunction.<sup>67</sup>

However, as these patients progress and they have more inflammation and breakdown of the cornea, their corneal sensation decreases as a protective mechanism. Therefore, if you ask neurotrophic patients how their eyes feel, they'll often say "not too bad," even in the presence of 4+ punctate epithelial erosions. There's a disconnect.

**Dr. Hovanesian:** What are some of the contributors that might indicate that you should test for corneal sensitivity? Are there any historical diseases or activities we should listen for?

TABLE 1. COMMON UNDERLYING CAUSES OF NK <sup>3</sup>					
Ocular factors	Systemic diseases	Other causes			
Herpes simplex	Diabetes	Alcoholism			
Herpes zoster	Stroke	Leprosy			
Previous ocular surgery	Prior neurosurgical procedures	Vitamin A deficiency			
Long-term contact lens wear	Aneurysm	Increasing age			
Long-term use of topical eye drops	Central nervous system diseases				
Chronic ocular surface disease	Multiple sclerosis				

**Dr. Whitley:** Herpes simplex and herpes zoster come to mind; herpes infections account for 27% to 32% of NK cases.<sup>8,9</sup> Patients with diabetes are at an increased risk as well.<sup>1,3</sup> Long-term contact lens wear and frequent use of topical drops with preservatives also beat up the ocular surface over years and are common contributing factors (Table 1).<sup>1,3</sup>

**Dr. Hovanesian:** Ocular surgery is another risk factor. I've also seen many cases of recalcitrant dry eye because we've damaged the limbal stem cells and corneal nerves through the chronic use of glaucoma medications with preservatives.

**CONSENSUS POINT #3:** Diagnosis of NK should hinge on testing for corneal sensation, ideally across the center and four quadrants

**Dr. Gupta:** Our patients with glaucoma take BAK-preserved medications for decades and we cannot stop these medications. Of course, there are newer preservative-free molecules that help with this, but I think preservatives are a common source we miss. We also need to think about systemic diseases. We currently have an epidemic of diabetes, and it is shocking how many patients don't check their blood sugar or don't know what their blood sugar is. Then there are neurologic causes such as acoustic neuroma surgery, transection of their nerves, and patients who have had other cranial facial procedures that have damaged the trigeminal nerve.<sup>3</sup> Sometimes patients don't elicit that they've had that these procedures, especially if it's an old injury, and eye doctors may have blinders onto the rest of the body. I always

TABLE 2. MACKIE CLASSIFICATION OF NK <sup>8,10</sup>				
Stage	Clinical features			
1	Corneal epithelial hyperplasia and irregularity Scattered small facets of dried epithelium Superficial punctate keratopathy Rose bengal staining of the inferior conjunctiva Increased viscosity of tear mucus Decreased break-up time Superficial neovascularization Stromal scarring Dellen			
2	Persistent corneal epithelial defect with smooth and rolled edges Descemet's membrane folds and stromal swelling Anterior chamber inflammatory reaction with hypopyon (rare)			
3	Corneal ulcer Corneal perforation Corneal stromal melting			
TABLE 3. PROPOSED CLASSIFICATION OF NK BY THE Neurotrophic keratitis study gr <u>oup1</u>				
Stage	Clinical features			
0	Altered sensation without keratopathy			
1	Epitheliopathy without stromal haze			
2	Epitheliopathy with stromal haze			
3	Persistent or recurrent epithelial defects			
4	Persistent or recurrent epithelial defect and stromal scarring without corneal ulceration			
5	Persistent or recurrent epithelial defect with corneal ulceration			
6	Corneal perforation			

think in the back of my mind, "Is there something along the course of that nerve that's causing dysfunction or an infectious or chemical process?"

**Dr. Hovanesian:** There are a couple of staging systems for NK— Mackie Classification and the Neurotrophic Keratitis Study Group (NKSG) classification.<sup>8-11</sup> There are important differences between each (Tables 2 and 3).

Early-stage disease in both classification systems relate to some form of corneal disruption, such as punctate epithelial keratopathy with reduced sensation. Altered sensation is a sine qua non early-stage disease in of both classification systems. Mackie stage 2 disease is persistent corneal epithelial defect with smooth and rolled edges—a classic NK defect. Mackie stage 3 is ulceration with or without perforation and stromal melting.

The NKSG has 6 classifications. Stromal haze has its own characteristic, putting the patient in a different staging category. Dr. Gupta, you were part of the NKSG. Can you discuss the thought process behind the 6 classifications?

**Dr. Gupta:** Parsing out haze formation was a major change. We see many patients in the clinic who are somewhere between Mackie stage 1 and 2 or Mackie stage 2 and 3. It's obvious when a patient has perforation. But we wanted to tease out haze formation within the classification because it's visually significant, requires more aggressive treatment, and is more time sensitive. It's very difficult to reverse corneal scaring once it occurs. We also wanted to highlight the persistent or recurrent nature of these defects between Mackie stage 2 and 3 disease. We need a better vocabulary when we discuss these patients now that we're looking for them.

**Dr. Perez Quinones:** I think we're going to continue to modify the Mackie Classification system as we are learning more about this condition thanks to experience we are gaining with the use of recombinant human neurotrophic growth factor (rNGF). We also need to make new recommendations on who we treat. I think the classification will need to be reclassified. How we treat the obvious disasters, the patients with perforation, won't change. But we need to rethink stage 1 disease and define it by corneal sensitivity. Does this patient have a neurotrophic component? It's going to come down to testing.

**Dr. Whitley:** The NKSG classification is more specific. Mackie is too broad; stage 1 means a lot of different things. Early identification is key with NK. The more specific we can get with staging regarding sensitivity, the better. Knowing how the nerves are functioning will help with proper diagnosis and treatment.

### CONSENSUS POINT #4: Classification of NK is moving away from the Mackie Classification system

#### **TREATMENTS FOR NEUROTROPHIC KERATITIS**

**Dr. Hovanesian:** We all would agree it's important to treat earlier stage disease because, if left untreated, it tends to progress. Corneal damage leads to further desensitization, which leads to further corneal damage. In many ways, the stage 1 patient is the most important patient to identify and treat. The nuance is in how we treat them. Let's talk about different treatments for a patient with corneal epitheliopathy with or without NK. Then tell us if there's anything you'd do differently for those patients you identify as having desensitized corneas. **Dr. Whitley:** Many patients present to our ocular surface clinic already on topical, over-the-counter or prescription therapies such as liftegrast or cyclosporine for many months or even years. If I see significant epitheliopathy when evaluating the ocular surface, I'm already adding stage 1 NK into the differential diagnosis, and I will check for corneal sensitivity. It's important to make sure that our technicians do not put any anesthetic prior to checking corneal sensitivity, I'm already considering the next step. For me, that's usually punctal occlusion along with amniotic membrane transplant (AMT) because I know autologous serum is not an option in my practice area. I don't do scleral lenses, so that's not an option either. Therefore, typically I go with AMT, as there are various studies showing the benefits of that for NK.<sup>8,12,13</sup>

**Dr. Skvarna:** I agree with Dr. Whitley. The only thing I'd add that's off-label and a little bit different is Muro 128 ointment at bedtime. One of our oculoplastic physicians tipped me off to it, and we have found that it helps tighten the corneal cells a little bit so they're not sloughing as much. I find that for some people, regular gels and ointments don't work, but that this works really well for them. I've found it to be very effective.

**Dr. Gupta:** Every NK patient comes in at different stages. The basics are to get them off every preservative they could possibly be on. I tell patients they'll need to use preservative-free tears every hour, knowing they'll have a 30% compliance rate. It's better than saying 4 times a day and having them do it once. I love the idea of ointments, and Muro 128 does help dehydrate those epithelial cells so they stick better, if that's an issue.

Punctal plugs are very helpful, as they essentially increase tear volume. I do like to treat inflammation before I put the plugs in or while I have the plugs in. Mainstream dry eye treatments such as cyclosporine and lifitegrast are all great initial molecules. You can quickly get those agents if you don't have AMT in your clinic. Topical steroids are very effective and quick at treating inflammation on the surface, which can drive epithelial breakdown. But you must first make sure there's no infectious etiology.

Going through their medication list is also helpful. Are they on an NSAID, and you didn't know it? Some patients come in with a baggie full of medicines, and they get confused and mix up the bottle tops. Going through each medication is critical.

**Dr. Perez Quinones:** It all comes down to if there's a neurotrophic component or not. One of my favorite go-to drugs when I see the epithelial changes and symptoms is autologous plasma. We built a plasma program, and it works very well.

**Dr. Hovanesian:** Is there a place for rNGF, cenegermin, in patients with stage 1 disease?

**Dr. Gupta:** I have used it in patients with severe stage 1 disease, bordering stage 2. It's very expensive however, and it's not easy to

get approved by insurance. There's lots of things to think about. My approach is to go through my list of exhaustive treatments— AMT, autologous serum tears, platelet rich plasma—everything. Many times, I will write a prescription for cenegermin and it will take several days to a few weeks to get approval. If we don't need it, we don't use it, but it's helpful to get the process started while treating the patient with what we have available. There are some data on using NGF in patients with Sjogren's disease, an extreme form of dry eye.<sup>14,15</sup> Phase 3 studies are underway at the moment, but there have been positive results in terms of treating the kind of keratitis and symptomatology that's found in these sort of severe dry eye patients.

**Dr. Perez Quinones:** The multicenter trials for cenegermin (REPARO and NGF0214) did not have corneal sensitivity as one of the main endpoints, although an improvement in corneal sensitivity was observed.<sup>16,17</sup> Some patients will develop pain, and it is a bigger proportion than what we thought. Having said that, maybe stage 1 and 2 disease is a crosstalk between the epithelium and the nerve. The elephant in the room is the insurance coverage and the cost.

**Dr. Hovanesian:** Yes, the elephant in the room is that the product is costly and there's a barrier in terms of getting insurance approval. However, if we accept that stage 1 disease is likely to progress, we need to think of what it will take to solve the problem for the patient.

**Dr. Perez Quinones:** It will take classifying the patient has having stage 1 disease and determining who will and won't progress. That comes down to the diagnosis. If you have a stage 1 disease where you really have decreased corneal sensation, you want to measure it and show the data that illustrate these patients are at high risk of progression. But presently there is a fine line between dry eye and stage 1 NK, and we need clarification there.

Dr. Whitley: Importantly, the pivotal trials for cenegermin were in stage 2 and stage 3 disease, but the agent is currently approved for all stages of NK. However, numerous retrospective studies have provided more information on the safety and efficacy of cenegermin in stage 1 disease, with others in progress. For example, Whitney Hauser, OD, presented results of the DEFENDO trial, which specifically evaluated the safety and efficacy of cenegermin in patients with stage 1 disease (n = 37), during the American Academy of Optometry meeting in December 2022.<sup>18,19</sup> Patients were given one drop of cenegermin 20 µg/mL, 6 times a day for 8 weeks and monitored at 4, 8, and 32 weeks. Efficacy endpoints included mean change in best-corrected distance visual acuity (BCDVA) a 15-letter gain in BCDVA from baseline to week 8, and improvement in corneal sensitivity at weeks 8 and 32. A total of 82.1% of patients reported improvement in corneal sensitivity through week 32, with 91.2% reporting improvement at week 8. BCDVA improved from baseline to week 8, and 15.2% of patients

gained 15 letters.<sup>18</sup> Eye pain was the most common adverse event (37.5%), which is in line with previously reported data.<sup>16,17</sup> A long-term follow-up study on DEFENDO is recruiting.<sup>20</sup> Patients with stage 1 NK who enrolled in the original DEFENDO study will be followed at months 24 and 30 posttreatment to evaluate long-term outcomes.<sup>20</sup>

Other retrospective trials on stage 1 disease include one from Yavuz Saricay et al (n = 17), which showed an improvement in corneal fluorescein staining and BCVA after 8 weeks of cenegermin treatment.<sup>21</sup> There were patients who had previously been treated with artificial tears (88.2%), autologous serum tears (47%), lifitegrast (47%), and tobramycin dexamethasone (47%). A little more than half reported mild to moderate ocular pain while taking cenegermin. Epitropoulos et al reported a retrospective case series of four adult patients with Mackie stage 1 NK who were treated with an 8-week course of cenegermin.<sup>22</sup> Three of the four patients experienced improvement in BCVA after treatment.

The point being that there is evidence that shows treating stage 1 disease with cenegermin improves vision and may prevent progression. We can order it for our stage 1 patients, but it does take time to get approval. In the meantime, we need to intervene by either aggressively treating the ocular surface with antiinflammatories or AMT to help heal and repair that epithelium.

**Dr. Hovanesian:** Is it reasonable to say that when we see OSD that is not responsive to initial therapy, we should test for corneal sensation and then consider cenegermin as part of treatment if corneal sensation is impaired and other therapies fail?

CONSENSUS POINT #5: Stage 1 NK should be treated with the intent of permanently improving or long-term improvement of the ocular surface

Dr. Skvarna: I would agree with that.

**Dr. Perez Quinones:** Yes, I agree. We have learned that there's a communication within the epithelium and the corneal nerve. So it's not about all the corneal nerve. I think recovering NGF is hitting some things that we don't understand, to be honest with you. Cenegermin has changed the way that we treat NK from not only healing but rehabilitation. I feel comfortable doing corneal transplants in all of these patients and being able to rehabilitate or resurface. There's something there, it's just a matter of how we quantitate it and how we understand it better to move forward.

**Dr. Hovanesian:** It's somewhat biphasic, isn't it? How many of you have seen that when you treat patients with cenegermin,

patients will experience increased pain or increased sensitivity of the cornea? That makes sense because if you're inducing corneal nerves that are now going to sense what they couldn't sense before. In the second phase, as the cornea heals, the patient will become more comfortable because there's a more stable surface.

**CONSENSUS POINT #6:** Maintenance therapy, ie, delivering ongoing nutrition to corneal nerves, remains an unmet need and newer therapies are being investigated in this regard

#### **THERAPIES IN THE PIPELINE**

**Dr. Hovanesian:** In the United States, cenegermin is the only agent approved by the US Food and Drug Administration for regenerating corneal nerves for NK. However, there are some other treatments in the pipeline such as insulin and other growth factors. What are your thoughts on these?

**Dr. Whitley:** For Mackie stage 1 disease, the nasal spray OC-01 (varenicline) is in phase 2 development (NCT04957758).<sup>23</sup> Oyster Point Pharma is also exploring an enriched tear film gene therapy approach (OCT-101) for NK Mackie stage 2/3 disease, which is in preclinical development.

**Dr. Gupta:** I've done a little bit of work with CSB-001 (NCT04909450) and RGN-259 (NCT05555589).<sup>24,25</sup> Regardless of the products that are being studied, I think what's valuable is that we have determined that there are novel pathways to amplify nerve regeneration. This is new and exciting information, but still in its infancy with lots of studies and room to grow. Ten years ago, if you asked us if we'd be able to reverse NK in these patients, I would have said that I'd believe it when I see it. Cenegermin is our first foray into this kind of nerve regrowth.

What's exciting is some of these future products are being considered for ongoing or maintenance therapy, which is our biggest unmet need. Right now, we have a product that we can use for 8 weeks once, maybe twice, in their lifetime if we're lucky with insurance coverage. What we need is to provide patients with severe disease an ongoing molecule that can provide nutrition to the nerve.

# CASE 1: SUCCESSFUL TREATMENT WITH CONVENTIONAL THERAPIES FOR CORNEAL DEFECT

**Dr. Hovanesian:** Our first case is a 42-year-old female with a history of a right-sided acoustic neuroma removal. She has mild facial weakness on the right, good lid closure with effort, and a 2 x 3 mm

inferior corneal oval defect with rolled edges. She is referred after 3 months of unsuccessful treatment with gentamycin QID, artificial tears QID, and petrolatum ointment at night. How would you approach this case?

**Dr. Gupta:** Neurosurgical procedures, such as acoustic neuroma excision, can lead to NK due to direct trauma to the trigeminal nerve. These patients can be difficult to treat and often have recurrent disease. In this case, I would start by placing an amniotic membrane graft to aid rehabilitation of the epithelial defect. I would also consider sending in a prescription for cenegermin as this medication can help to repair the impaired nerve function. The patient retains reasonable lid closure function, so I would not consider tarsorrhaphy at this time.

Dr. Skvarna: I would begin by taking a complete history, looking for any evidence of DED, long-term use of topical eye drops, long-term contact lens wear, previous ocular surgery, exacerbating medical conditions, and an assessment of how long has patient had this condition. I'd also look for nocturnal lagophthalmos and assess corneal sensitivity and the lids. If the patient does have NK, I'd determine the stage and identify any other exacerbating conditions. For a treatment plan, if it is NK, I'd consider forced closure with mask or tarsorrhaphy if lid closure is incomplete at bedtime. Regardless of how well a treatment works, if lids are not closing it will be difficult to manage this patient. Once lid closure is successfully managed, I'd consider AMT, especially if condition is short term and patient has adequate corneal sensitivity. Finally, I'd consider cenegermin 6 times a day for 8 weeks if sensitivity is absent and the PED does not heal with aggressive treatment including forced lid closure.

**Dr. Whitley:** This patient has several options, but cenegermin would be ideal. We could add punctal occlusion and/or hydrogel contacts and autologous serum. I have limited experience with autologous serum due to limited labs available in our area. In this case, I'd consider a cryopreserved amniotic membrane in addition cenegermin.

**Dr. Perez Quinones:** I agree with Dr. Whitley. This is the ideal patient for cenegermin.

#### **CASE 2: PERSISTENT CORNEAL EPITHELIAL DEFECT**

**Dr. Hovanesian:** Our next case is a 78-year-old male patient with cataract and longstanding chronic open-angle glaucoma who recently underwent uncomplicated cataract surgery in his left eye. He's dissatisfied with the visual outcome. His past ocular history includes cataract surgery with a monofocal implant 3 months ago and open-angle glaucoma treated with many years of topical latanoprost (now generic formulation). His exam shows BCVA 20/70, stippling of stain across central and inferior cornea, and vascularized limbus (Figure). How would you approach this patient?



Figure. Corneal staining showed 3+ SPK OS and punctate erosions. Image originally published in *Cataract & Refractive Surgery Today.* 

**Dr. Perez Quinones:** This is a potential new population of patients who have no obvious neurotrophic component, but who have persistent corneal epithelial defect. Cenegermin can be used for these patients.

**Dr. Gupta:** Patients with glaucoma who are medically treated have a cumulative high chronic exposure to preservatives such as BAK. This can lead to toxicity in the cornea and gradual NK. In these cases, it is important to reduce the preservative load and also test corneal sensation. Conservative measures include lubrication with preservative-free tears, adding preservative-free ointment, and also considering a topical steroid to see if it will reduce the chronic surface inflammation, all while trying to eliminate further BAK exposure.

**Dr. Whitley:** Anytime we see a patient with glaucoma, we must evaluate for ocular surface comorbidities. This patient recently had cataract surgery with persistent postoperative OSD with decreased K sensitivity. I would treat the ocular surface with topical anti-inflammatories and address meibomian glands, as we know there is a high prevalence of meibomian gland dysfunction in patients with glaucoma. Unfortunately, the patient already had surgery, and we missed the opportunity for a MIGS device. I'd consider selective laser trabeculoplasty (SLT) or preservative-free glaucoma medication and/or intracameral bimatoprost. If OSD treatments have not improved the surface, I'd consider AMT to the left eye while waiting for cenegermin authorization.

**Dr. Skvarna:** My first consideration would be to change to nonpreserved glaucoma medications or refer patient to glaucoma specialist to consider having an SLT or other glaucoma procedure (preferably noninvasive) to lower pressures. Preservative-free tears throughout the day could possibly improve the corneal surface. If it doesn't, I would consider a very short course of nonpreserved loteprednol. AMT and cenegermin are other options if there's no improvement with the previous treatments.

# CASE 3: MILD INFERIOR CORNEAL STAINING IN REFRACTIVE SURGERY CANDIDATE

**Dr. Hovanesian:** Our last case is a 58-year-old male patient who underwent uncomplicated LASIK surgery 25 years ago. He presents now to consider further surgery for better uncorrected near vision. He has no complaints other than needs reading glasses. Upon exam, he has mild inferior staining in both eyes, which is not improved with 2 weeks of artificial tear treatment. What are your next steps?

**Dr. Perez Quinones:** This is an interesting scenario. If this patient has a neurotrophic component to the staining, then cenegermin will help. However, cost will may represent a limiting factor.

**Dr. Skvarna:** My first step is to ascertain whether or not the patient has any prior ocular or medical history that will lead to dry eyes other than LASIK. I'd do complete anterior segment workup including osmolarity, MMP-9, meibography, and corneal sensitivity testing. I would also check for lagophthalmos. Depending on the findings, I would consider a nighttime gel or ointment, a short course of steroids, and possibly an immunomodulator and or meibomian gland treatment prior to additional refractive surgery. It is possible that the patient has decreased corneal sensitivity due to prior LASIK, and it would be nice to see research to determine if pretreating with cenegermin would decrease corneal hypoesthesia postrefractive surgery.

**Dr. Whitley:** After 2 weeks of artificial tears, I would do a full dry eye workup. Due to the inferior corneal staining, I would perform the Korb-Blackie lid light test to evaluate for incomplete lid seal. If found, I'd consider preservative-free ointment or taped tarsor-rhaphy. My next consideration would be DED with my work up including K sensitivity. Due to the mild presentation, I would start with anti-inflammatories, then follow-up in 4 to 6 weeks. I would add therapies according to TFOS DEWS II while addressing both evaporative and aqueous deficient component.<sup>26</sup> Punctal plugs would be a consideration as well. If no improvement after a couple months, I'd reassess K sensitivity and if no improvement, I would consider AMT and/or cenegermin.

**Dr. Hovanesian:** Thank you to all the faculty for your valuable insights today. To summarize, NK overlaps with what we routinely see as OSD in our clinics, and it may have a greater role in nonresponders to traditional therapy than we think. Therefore, corneal sensitivity should be performed as part of the dry eye workup, particularly for patients who are nonresponders to conventional therapy for OSD. Stage 1 NK should be treated with an aim of success, which means long-term improvement the ocular surface so that we do not see progressive disease. Data show that cenegermin works for stage 1 disease. Cenegermin should be considered when patients don't respond to conservative therapy, when the cost is justified by the benefit. We should keep our mind open to future therapies in development that may change the landscape of treatment of NK in the future.

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# Consensus Panel Highlights: Updated Approaches to Neurotrophic Keratitis Staging and Treatment

Release Date: August 28, 2023 CME Expiration Date: September 2024 COPE Expiration Date: August 28, 2024

#### **INSTRUCTIONS FOR CREDIT**

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DEMOGRAPHIC INFORM Profession MD/DO OD NP NP	Years in Practice       > 20       11-20       6-10	Patients Seen Per Week (with the disease targeted in this educational activity) 0	Region Midwest Northeast Northwest	
Nurse/APN PA Other	<1	1-15 16-30 31-50 >50	Southeast Southwest	
LEARNING OBJECTIVES	ì			
Did the program meet the	e following educational objectives?	Agree	Neutral	Disagree
<b>Explain</b> diagnostic strategie stage 1 disease	s for neurotrophic keratitis (NK) and ider	tify patients with		

to traditional treatments

### **POSTTEST QUESTIONS**

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to develop personalized treatment plans for patients with stage 1 neurotrophic keratitis (NK) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

- A. 1
- B. 2
- C. 3
- D. 4
- E. 5

2. All of the following statements about the prevalence of NK are true EXCEPT:

- A. NK has historically been thought of as an extremely rare disease
- B. NK has traditionally been diagnosed in stage 2 or stage 3 of the disease
- C. Stage 1 NK is much more prevalent than has historically been thought
- D. Stage 1 NK is extremely rare

# 3. A 64-year-old patient with a history of dry eye disease (DED) presents to your clinic for his third follow-up. He has been treated with artificial tears, punctal plugs, and cyclosporine with no significant improvement in exam findings. On exam, you note 2+ staining and epitheliopathy. The patient states that his eyes feel fine. Which of the following is a reasonable next step in management?

- A. Suspect DED and escalate dry eye therapy
- B. Suspect herpetic keratitis and initiate antiviral therapy
- C. Consider NK and test for corneal sensitivity
- D. Consider blepharoplasty

# 4. All of the following statements regarding corneal sensitivity testing are true EXCEPT:

- A. Cotton wisp testing is a reasonable testing method for corneal sensitivity
- B. Wax dental floss is a reasonable testing method for corneal sensitivity
- C. It is important to test all corneal zones when testing for corneal sensitivity
- D. Testing central corneal sensation is adequate when testing for corneal sensitivity

# 5. You are evaluating a patient with punctate epitheliopathy. Cotton wisp testing reveals decreased corneal sensitivity. All of the following are reasonable treatment options for this patient EXCEPT:

- A. Punctal occlusion
- B. Amniotic membrane transplant
- C. Autologous serum drops
- D. Topical ketorolac

#### 6. A patient with stage 1 NK presents to your clinic. He continues to progress despite treatment with frequent preservative-free artificial tears and punctal occlusion. All of the following options are reasonable next steps EXCEPT:

- A. Oral steroids
- B. Topical cyclosporine or lifitegrast
- C. Autologous serum drops
- D. Topical steroids

#### 7. What stage NK can cenegermin be used for?

- A. Stage 1
- B. Stage 2
- C. Stage 3
- D. All of the above

8. A 42-year-old patient with a history of right-sided acoustic neuroma removal with resulting right-sided facial weakness presents to your office with a 2 mm x 3 mm inferior corneal oval defect with rolled edges. She has been on gentamycin QID, artificial tears QID, and ointment at night for 3 months without significant improvement. All of the following are reasonable treatment options for this patient EXCEPT:

- A. Consider amniotic membrane transplant
- B. Consider cenegermin
- C. Consider tarsorrhaphy
- D. Continue current regimen

9. A 78-year-old patient with a history of cataract surgery and primary open-angle glaucoma presents to your office for evaluation. He had cataract surgery 3 months ago and has been on latanoprost qhs OU for many years. Examination shows inferior corneal staining. Which of the following statements about this patient is true?

- A. Chronic exposure to benzalkonium chloride (BAK) from this patient's glaucoma drops can lead to gradual NK
- B. This patient is unlikely to have NK
- C. Latanoprost drops have a low BAK content and are optimal for patients with NK
- D. This patient is not a candidate for cenegermin

## 10. Which of the following statements about ocular surface disease (OSD) and NK is TRUE?

- A. OSD is separate from NK with very different exam findings
- B. NK often overlaps with OSD in exam findings, and corneal sensitivity testing can help differentiate the two conditions
- C. OSD presents with epitheliopathy while NK presents with an epithelial defect
- D. OSD and NK are clinically indistinguishable

#### 11. A 58-year-old patient with a history of LASIK presents for repeat refractive surgery evaluation. On examination, he has mild inferior staining in both eyes that has not improved with 2 weeks of artificial tear treatment. What is the best next step in management for this patient?

- A. Schedule refractive surgery
- B. Schedule tarsorrhaphy
- C. Full DED workup, lid evaluation, and corneal sensitivity testing
- D. Observation

### **ACTIVITY EVALUATION**

Your responses to the questions below will help us evaluate this activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to particip	ating in this course: 5 = High, 1 = Low		
Rate your knowledge/skill level after participati	ng in this course: 5 = High, 1 = Low		
This activity improved my competence in mana	iging patients with this disease/condition/symptom YesNo		
Probability of changing practice behavior based	on this activity:High LowNo change needed		
If you plan to change your practice behavior, w	hat type of changes do you plan to implement? (check all that apply)		
Change in pharmaceutical therapy	Change in nonpharmaceutical therapy		
Change in diagnostic testing	Choice of treatment/management approach		
Change in current practice for referral	Change in differential diagnosis		
My practice has been reinforced	I do not plan to implement any new changes in practice		
Please identify any barriers to change (check all tha	t apply):		
Cost	Lack of consensus or professional guidelines		
Lack of administrative support	Lack of experience		
Lack of time to assess/counsel patients	Lack of opportunity (patients)		
Reimbursement/insurance issues	Lack of resources (equipment)		
Patient compliance issues	No barriers		
Other. Please specify:			
The design of the program was effective for the co	ntent conveyed Yes No		
The content supported the identified learning objectives Yes No			
The content supported the identified learning obje			

The content was free of commercial bias	Yes	No
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The faculty was effective	Yes	No
You were satisfied overall with the activity	Yes	No
You would recommend this program to your colleagues	Yes	No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

- \_\_\_\_\_ Patient Care
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- \_\_\_\_\_ Professionalism
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Additional comments:

This information will help evaluate this activity; may we contact you by email in 3 months to inquire if you have made changes to your practice based on this activity? If so, please provide your email address below.



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