January/February 2022

evolve medical education

A CE activity administered by Evolve Medical Education LLC.
This activity is supported by unrestricted educational grant from Dompé.

Sponsored by
UAB SCHOOL OF OPTOMETRY
The University of Alabama at Birmingham

NEUROTROPHIC KERATITIS:
The Latest Approaches in Diagnosis, Classification, and Treatment

KELLY K. NICHOLS, OD, MPH, PHD, FAAO
Program Chair
Professor and Dean
The University of Alabama School of Optometry
Birmingham, AL

DOUGLAS K. DEVRIES, OD
Co-founder
Eye Care Associates of Nevada
Sparks, NV

FRANCIS S. MAH, MD
Director of Corneal and External Disease
Co-director of Refractive Surgery
Scripps Clinic
La Jolla, CA

Supplement to
MODERNOPTOMETRY

Release Date: Jan. 7, 2022
COPE Expiration Date: Jan. 6, 2024

NEUROTROPHIC KERATITIS: The Latest Approaches in Diagnosis, Classification, and Treatment

Content Source

This continuing education (CE) activity captures content from a live virtual symposium.

Activity Description

Neurotrophic keratitis (NK) can lead to epithelial breakdown, impairment of healing, and ultimately to the development of corneal ulceration, melting and perforation. The faculty discuss the potential causes of NK, how to differentiate it from similar diseases, and when referrals may be necessary. Treatment options are also discussed, including the mechanisms of action of newer therapies and when they should be introduced.

Target Audience

This certified CE activity is designed for optometrists.

Learning Objectives

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

- **Describe** the stages of NK, and how to differentiate it from similar diseases
- **Recognize** the various potential causes of NK and when referrals may be necessary
- **Summarize** mechanisms of action of newer treatments and when they should be introduced into treatment regimens for NK
- **Identify** the relationships between disease characteristics, drug, treatment frequency, visual and anatomic outcomes

Grantor Statement

This activity is supported by unrestricted educational grant from Dompé.

Evolve Medical Education LLC (Evolve) is an approved COPE administrator.

This activity, COPE Activity Number 123133, is accredited by COPE for continuing education for optometrists for 1.0 hour.

Course Approval: 76275-AS

Activity Approval: 123133

To Obtain Credit

To obtain credit for this activity, you must read the activity in its entirety and complete the Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit http://evolvemeded.com/course/2151-supp. Upon completing the activity and self-assessment test, you may print a CE credit letter awarding 1.0 COPE Credit. Alternatively, please complete the Posttest/Activity Evaluation/Satisfaction Form and mail or fax to Evolve Medical Education LLC, 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950.

Disclosure Policy

It is the policy of Evolve that faculty and other individuals who are in the position to control the content of this activity disclose any real or apparent conflicts of interest relating to the topics of this educational activity. Evolve has full policies in place that will identify and resolve all conflicts of interest prior to this educational activity.

Cover image courtesy of Francis S. Mah, MD.

The following faculty/staff members have the following financial relationships with commercial interests:

Douglas K. Devries, OD, has had a financial agreement or affiliation during the past year with the following commercial interest in the form of *Advisory Board*: Alcon, Allergan, Avelino, Akorn, Azura, Bausch + Lomb, BlephEx, Bio Tissue, Bruder, Eyevance, Kala Pharmaceuticals, Johnson & Johnson Vision, Novartis, OcuSoft, Quidel, Sight Sciences, Science Based Health, Sun Pharmaceutical Industries, Tarsus, Tearlab, Thea, and Visus. *Speaker's Bureau:* Allergan, Bausch + Lomb, Bio Tissue, BlephEx, Bruder, Eyevance, Kala Pharmaceuticals, Lumenis, Johnson & Johnson Vision, OcuSoft, Sight Sciences, Science Based Health, Sun Pharmaceutical Industries, and Tearlab. *Stock/Shareholder:* RPS.

Francis S. Mah, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: Alcon Vision, Allergan, Bausch + Lomb, Eyenovia, Glaukos, iView, Johnson & Johnson Vision, Nevakar, Novartis, Ocular Science, and RxSight..

Kelly K. Nichols, OD, MPH, PhD, FAAO, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: Bruder, Dompé, HanAll Bio, Kala Pharmaceuticals, Novartis, Osmotica, Oyster Point Pharma, Sight Sciences, Thea, Tarsis, and Topivent. *Grant/Research Support:* Allergan, Kala Pharmaceuticals, NIH, and Tear Science. *Stock/Shareholder:* Alcon Vision, Acquiom, LacriScience, and Tear Film Innovations.

Editorial Support Disclosures

The Evolve staff and planners have no financial relationships with commercial interests. Michelle Dalton, writer, has no financial relationships with commercial interests.

Off-Label Statement

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of Evolve, *Modern Optometry*, or Dompé.

Digital Edition

This supplement is part of a larger curriculum, which also includes two webinars. Go to https://evolvemeded.com/course-group/patient-care-update-neurotrophic-keratitis-diagnosis-treatment-and-referrals to view the related activites.

To view the online version of the supplement, go to http://evolvemeded.com/course/2151-supp.

PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for credit.

1. Please rate your confidence in your ability to describe the mechanisms of action of newer treatments and when they should be introduced into treatment regimens for 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. Ms. Smith is referred into your clinic for a dry eye evaluation. She has a history of type 2 diabetes, proliferative diabetic retinopathy, and bacterial corneal ulcers with poor healing that required penetrating keratoplasty; 2 months later the epithelium has not yet healed. Previous treatments included antibiotics, steroids, bandage contact lenses, and self-retaining amniotic membrane. Corneal sensitivity testing reveals centrally absent sensation. What would be considered an appropriate next step?

a. Continue with biologic corneal bandage
b. Increase steroid-free artificial tears to 5 times daily
c. Initiate a 6-week course of cenegermin 8 times daily
d. Initiate an 8-week course of cenegermin 6 times daily

3. _____ is a hallmark clinical test to diagnose NK.

a. Visual acuity testing
b. In vivo confocal microscopy
c. Corneal sensation testing
d. Imaging with a slit lamp

4. Corneal innervation is essential for good epithelial health. How do corneal nerves maintain a healthy corneal surface?

a. Provide stromal, epithelial, and Bowman's structural support
b. Maintain sensory functions that are essential to tear film maintenance
c. Facilitate protective functions of blinking and tear production as well as trophic support
d. Provide key nutrients to the epithelium while also serving as a physical barrier to microbes

5. Endogenous nerve growth factor helps preserve and restore the ocular surface by which of the following mechanisms?

a. Strengthening tight junctions between epithelial cells to enhance corneal epithelial barrier functions
b. Providing nutrition to conjunctival goblet cells and eyelid tear glands in order to increase tear production and improve tear quality
c. Stimulating limbal stem cells to generate new epithelial cells
d. Increasing tear production at the lacrimal gland, stimulating nerve regeneration, and supporting epithelial cell proliferation and differentiation

6. NK results from damage to which of the following nerves?

a. Oculomotor Nerve (CN III)
b. Trochlear Nerve (CN IV)
c. Trigeminal Nerve (CN V)
d. Abducens Nerve (CN VI)
e. Facial nerve (CN VII)

7. Rank in order from greatest to least the areas of highest corneal sensation:

a. Inferior limbus> temporal limbus> central cornea
b. Temporal limbus> central cornea> inferior limbus
c. Central cornea> temporal limbus > inferior limbus
d. Central cornea> inferior limbus > temporal limbus

8. Which of the following steps should be utilized while performing corneal sensitivity testing?

a. Check both eyes
b. Test in the center and all four quadrants of the cornea
c. Apply topical tetracaine first, then check sensitivity
d. All of the above
e. A+B

9. What treatment options are available for NK?

a. Amniotic membrane
b. Autologous serum tears
c. Scleral lenses
d. Cenegermin
e. All of the above

10. What was the most common adverse event seen in clinical trials with cenegermin?

a. Foreign body sensation
b. Eye pain on instillation
c. Ocular Inflammation
d. Tearing
e. Corneal deposits

11. In the European cenegerimin trial, what percentage of patients who healed after one 8-week course of treatment remained healed at 1 year?

a. 70%
b. 75%
c. 80%
d. 85%

12. Complete corneal healing, defined as 0 mm staining in the lesion area and no other persistent staining in the rest of the cornea after 8 weeks of treatment, was achieved in what percentage of patients receiving cenegermin in the European Trial?

a. 45%
b. 55%
c. 65%
d. 75%

NEUROTROPHIC KERATITIS: THE LATEST APPROACHES IN DIAGNOSIS, CLASSIFICATION, AND TREATMENT

Neurotrophic keratitis (NK) is an orphan disease, affecting fewer than 1.6 per 10,000 people.[1,2] NK develops in 6.0% of patients with herpes simplex keratitis, 12.8% of patients with herpes zoster keratitis, and 2.8% of patients with postsurgical nerve damage.[1,2] Taken together, there are only about 65,000 cases in the United States. However, its actual incidence is likely much higher because it's frequently un- or misdiagnosed.[3] Several chronic diseases, such as dry eye syndrome, exposure keratopathy, contact lens-related disorders, and others, may mimic NK. Further, although expert opinions on its diagnosis and treatment have been published in the literature, no formal guidelines exist, making NK a particularly challenging eye disease. Early diagnosis and severity-based treatment are keys to recovery and preventing further corneal damage. The following panel discussion summary showcases experts in the management of NK as they discuss diagnostic strategies, its stages, and current treatment options.

— Kelly K. Nichols, OD, MPH, PhD, FAAO

UNDERSTANDING NEUROTROPHIC KERATITIS

Defining Neurotrophic Keratitis

Dr. Nichols: NK is a degenerative corneal disease in which there is damage to the trigeminal nerve that results in a loss of corneal sensation.[4] The hallmark of NK is decreased or no sensation in the presence of corneal irregularities/damage. This is different from neuropathic pain, in which you have a patient who is extremely symptomatic, but who has no staining on ocular surface tests, otherwise known as pain without stain. The corneal damage and loss in sensation are the resultant breakdown of the corneal epithelial layer that comes with impaired corneal healing, persistent epithelial defects, corneal ulceration, stromal melting, and perforation. These are the patients you remember in the middle of the night, hoping you're treating them as best as you can.

You want to take a particular look at patients who have dry eye contact lens-related disorders, blepharitis, exposure keratopathy, stem cell deficiency, topical drug toxicity, and chemical injury because they might have concurrent disease or undiagnosed NK.[1,5]

Corneal Innervation

Dr. Nichols: We all know how sensitive the cornea is; in fact, it's thought to be the most innervated tissue in the human body.[6,7] The innervation pattern isn't just for the sensation aspect, it's critical to the maintenance of the ocular surface homeostasis, which includes tear film homeostasis as well. The corneal epithelial cells are in a supportive relationship with the corneal nerves.[1,2] They work together. Any deficits in either creates a feedback loop, which can make things worse. We know the corneal nerves maintain the corneal integrity, and they cause the important protective functions like blinking. If you get something in your eye, you're going to blink and tear, assuming those nerves can generate those signals. Also importantly, there's trophic support, neuropeptides, substance P—all these things are floating around in the tear film and are in the tissues promoting cell proliferation, migration, and adhesion, which maintain that smooth barrier on the ocular surface. If there's damage to the corneal nerves and thereby a loss of corneal sensation, then you get a feedback loop in which you have epithelial breakdown and poor healing. The cycle continues.[6,7]

The Etiology of Neurotrophic Keratitis

Dr. Nichols: There are a number of things that can be related or have been shown to be associated with NK, such as herpes simplex and zoster, diabetes, and certain topical medications that are used for common conditions like glaucoma.[1] I see a lot of diabetic eye disease in my practice. Stepping back to think about the concurrent possibility of having NK associated with a diabetic patient is important. There can be long-standing corneal dystrophies. Fifth-nerve palsy can lead to NK as well.[2,5] You have to keep all this in the back of your mind. If you have a new patient or you haven't gone through his or her history with NK in mind, it may be worth revisiting some of these aspects. You can have a patient with diabetes who develops NK who also has dry eye or might be taking glaucoma medications. Dry eye, blepharitis, topical drug toxicity, and limbal cell deficiency are just a few examples of comorbidities that can confound the diagnosis of NK and worsen the prognosis.[5] This is why a thorough diagnostic exam and workup, while always being considerate of some of these underlying etiologies, is very important.

To summarize, there are two different things related to the nerve malfunction, which is central to NK: impairment of trophic supply and impairment of trigeminal reflexes.[4] Impairment of trophic supply leads to corneal epithelial alterations and impairment of corneal healing. This is important because that's what keeps the cells talking to one another and maintaining their adhesions in being able to heal themselves. Impaired trigeminal reflexes reduces tear film production and blink rate. All these things taken

together will result in corneal epithelial breakdown. That process needs to be halted so that you can return to the normal homeostasis, and things can begin to work together again.

Causes of impaired trigeminal nerves include strokes, brain tumors, LASIK or other ocular surgery, chronic use of topical medications, and corneal dystrophies.[5] Strokes and brain tumors may not be top of mind when you're looking at a patient with NK, but topical medication use and corneal dystrophies should be.

Clinical Presentation of Neurotrophic Keratitis

Q | **Dr. Nichols:** What is the most important thing to you in the clinical presentation of NK? What are you looking for?

Douglas K. Devries, OD: As you were going through the list of different systemic conditions that should trigger a starting point of an NK diagnosis, it occurred to me that we need to roll back our thinking from end-stage NK, which is a neurotrophic ulcer, to the beginning stages. Where does NK start, and how does it evolve? Does the patient have diabetes? Have they had refractive surgery? Are they a long-time wearer of contact lenses? So many of these cases present in the practice every single day and you have to keep your mind open to some of the causes. A case history is critical in triggering that thought process.

Francis S. Mah, MD: That's a great point, Dr. Devries. I'm going to go one step further. You can't make the diagnosis unless it's part of your differential. If you're not thinking about it, then you'll never make the diagnosis; it has to be top of mind. It's a no-brainer to identify the persistent epithelial defects and the corneal ulcerations that might represent NK. But how do we identify them earlier? In addition to thinking about it, I think we need to test for it. I've started checking corneal sensation in every person who walks in with the potential of ocular surface disease. Even if it's a simple dry eye consult, I check for corneal sensation. We have to start somewhere. People just don't walk in with a corneal ulcer, and that's the beginning. The beginning is decreased sensation and the epithelium intact.

Dr. Nichols: That's a fantastic tip, and I hope readers start to incorporate corneal sensation testing as part of their ocular surface exam. This is an easy thing you can do. Dr. Devries will go over some methods for conducting that testing in the clinic, but before we get there, is there anything else that you'd like to add about the early clinical presentation of NK?

Dr. Devries: Decreased sensation is an early symptom. But, as we all know, signs and symptoms of ocular surface disease don't always correlate. Why is that? Why do you see these corneas that are absolutely horrible and the patient doesn't have this sensation? Their complaints are typically vision related, that they can't get a consistent prescription. The whole idea of stain without pain is something we must keep in mind. The biggest change I've made within my practice is establishing what is normal versus abnormal corneal sensitivity to answer some of these questions. Neurosensory abnormality was recently added to some definitions of ocular surface disease, which is incredibly important[8]; it helps us understand why signs and symptoms don't always align.

If we see any recalcitrant punctate epithelial keratopathy (PEK), that should alert us to do some tests. Because when it becomes more pronounced with a persistent epithelial defect, when we start having stromal involvement, when we start to see melting and perforations, that's advanced NK. I think our challenge as clinicians is, how early can we be on the lookout to establish this as part of the differential diagnosis?

DIAGNOSTIC CONSIDERATIONS FOR NEUROTROPHIC KERATITIS

Dr. Devries: Taking clinical history is critical to diagnosing NK. One that's pretty obvious is someone on a prostaglandin analogue, which we know decreases some corneal sensitivity. That's why those patients develop profound dry eye at such a high percentage. Corneal sensitivity testing must become a routine part of our ocular surface disease workup. Other diagnostics include a complete eye exam, corneal staining, corneal cultures to rule out bacterial infection, in vivo confocal microscopy, and an evaluation for autoimmune disease and other systemic immune disorders.[5] Of course, you're going to look at staining, and you're going to do some of the other tests. You may or may not want to do a Schirmer test.

Taking a good history, testing corneal sensitivity, staining, and looking at the cornea are important. When we look at NK, it really is impaired function of the fifth cranial nerve. That can happen in many different ways, but it starts with reduced corneal sensitivity. That initial phase we see may not be a persistent epithelial defect per se; it could be recalcitrant PEK that will not heal, and that patient is not responding to the typical treatment that would address that in ocular surface conditions. When we start seeing recalcitrant PEK, we should start looking at corneal sensitivity and see if that is perhaps one of our differential diagnosis. Because if not, it will lead to that persistent epithelial defect that will not heal and eventually go on to become a corneal ulcer. We certainly want to identify it at a much earlier stage. In the primary optometric practice, we're in a perfect position to be able to identify those much earlier.

In looking at some of the facts about corneal sensation, it tends to be greatest in the central cornea. However, in elderly patients, it is more sensitive in the periphery.[9-11] It does tend to drop as we get down to the limbus, and it falls with age as well. It's not effected by iris color, and tends to be more sensitive in the temporal limbus and inferior limbus. Just like all these neuropathic disorders in diabetes, we tend to see reduced corneal sensation in diabetic patients.

How to Test for and Document Corneal Sensitivity

Dr. Devries: When a patient comes in with herpes that has affected one eye, it's very easy to tell the difference in corneal sensitivity because you can clearly see the decrease between the affected and unaffected eye. But what about patients who have a bilateral decrease in corneal sensitivity? Now you don't have that

ability to test a normal eye against an abnormal eye. I strongly encourage everyone to test normal patients within your practice so you can see what a normal corneal blink reflex is when you do sensitivity testing. This helps determine a baseline. You can do it qualitatively with a cotton swab, cotton wisp, dental floss, or a tip of a tissue, or quantitatively with a Cochet-Bonnet esthesiometer. Most of us are going to use the qualitative method because we don't have a Cochet-Bonnet esthesiometer.

I like to use a piece of dental floss that I wrap around forceps so I have a consistent length of floss. I test each of the four quadrants (superior, temporal, inferior, and nasal) and note if it's normal or abnormal relative to baseline. You'll have to develop your own basic scoring system because there isn't a specified method for corneal sensitivity testing. It's up to you to determine what method you want, and then you document that there's decreased sensitivity. I like to have as much information as possible, but you can simply document a decreased sensitivity based on the method you decide to perform in your clinics. But establishing a baseline is critical.

Dr. Mah: I agree with Dr. Devries. The key message is to test the corneal sensitivity of every patient. I use a cotton tip applicator to test the four quadrants. If you use dental floss, make sure to use unwaxed and unflavored floss, otherwise you'll be stimulating some nociceptors on the cornea. You can also use the tip of a tissue; each method accomplishes the same thing.

I classify the sensitivity as anesthesia, hypoesthesia or decreased, and normal. You also want to check both eyes so you have that baseline, especially if there's an eye you're suspicious about. You can test only the center or the four quadrants. The four quadrants, theoretically, will help you better identify masqueraders such as herpes zoster and herpes simplex conditions.

Q | **Dr. Nichols:** Do you perform these tests in free space or behind the slit lamp?

Dr. Mah: I usually use a slit lamp now because I've become presbyopic, but I used to do it in free space. In general, I think there are some people who will start blinking before you've done anything. If you have one of those patients, then it's a bit more difficult.

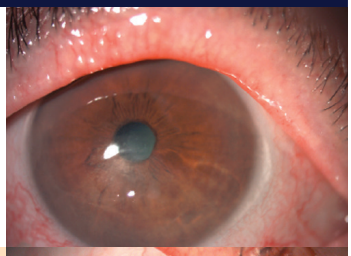
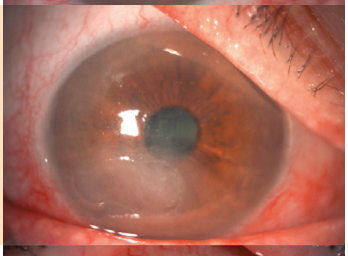
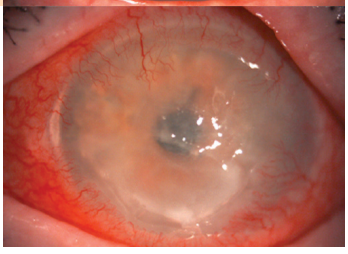
Dr. Nichols: How do you hold the forceps and prepare the floss?

Dr. Devries: I hold the forceps horizontally and come in at an angle to avoid the lashes. If you hold the forcepts vertically and you touch the lashes, the patient will reflectively blink. I also perform the test behind the slit lamp for expediency. The test is extremely fast once you become proficient.

Dr. Nichols: Do you wrap the floss before you start the exam?

Dr. Devries: Yes, I wrap it around and it stays. I use tape so there's a consistent link. When I switch hands, I also turn it so it's pointed toward the cornea. I keep it consistent so I can measure that difference between the two eyes.

TABLE 1. Mackie Severity Classification for Neurotrophic Keratitis[1,33]

STAGE	CLINICAL FEATURES	EXAMPLE
1	• Punctate epitheliopathy (punctate corneal fluorescein/LG staining) • Decreased TBUT • Stromal haze	
2	• Persistent epithelial defect with smooth rolled edges • Stromal opacity	
3	• Stromal thinning/ulceration • Corneal perforation	

Mackie Classification

Dr. Devries: The Mackie Severity Classification segments NK into three stages: stage 1, stage 2, and stage 3 (Table 1).[1] We lump quite a bit into three stages. Stage 1, for example, can have punctate epitheliopathy and also some stromal haze, but it doesn't necessarily have to be present. There can also be decreased tear breakup time (TBUT). Stage 2 is classified as a persistent epithelial defect that is open on the cornea that won't heal. Those cases are very frustrating. As you look at that cornea, you start thinking about your patients who have diabetic foot ulcers and other wounds that won't heal. That's when you start to really see some stromal opacity underneath those persistent epithelial defects. Stage 3 is neurotrophic ulcer. That's when you're starting to get thinning ulceration. Of course, the worry then is corneal perforation.

Breaking this down further, stage 1 patients typically have a rose bengal staining of the palpebral conjunctiva, decreased TBUT, and increased mucous viscosity.[12] We often see this as recalcitrant corneal epithelial defects that just don't want to heal. They tend to resemble dry eye patients. Since dryness can be an accelerant, that's where we need to start looking at differentiation to see if there's a neurotrophic component. Measuring corneal sensitivity is a great way to do that.

Patients with stage 2 disease have an epithelial defect, as illustrated in Table 1. You can see that typically oval inferior defect surrounded by a rim of loose epithelium, and the edges could very well be smooth and rolled. This is one of those defects that as you

try to heal with a bandage contact lens, it just doesn't want to heal. These patients may also have an anterior chamber inflammatory reaction as well. Stage 3 patients have a corneal ulcer with potential melting and perforation.

New Classification From the Neurotrophic Keratitis Study Group

Dr. Devries: The challenge with the Mackie classification is we've clustered a number of distinct and often nonsequential phases of NK development into three categories that are too broad and nonspecific. To address this need, the Neurotrophic Keratitis Study Group (NKSG) have proposed a new 7-step clinical staging system (submitted for publication). Dr. Mah, you were part of that team. What can you tell us about that classification system?

Dr. Mah: As you mentioned, the issue with the Mackie classification is that it was originally described decades ago. Although it's been extremely helpful, there's a lot that happens between Mackie classifications 1 and 2 and 2 and 3.[12] The members of the NKSG, chaired by Dr. Edward J. Holland, attempted to do several things. First, they tried to help define the stages of each episode that happens clinically and include more descriptions of the various different changes that occur. In addition, the group tried to update the definition of NK as well as some of the testing that's involved, including those we discussed earlier regarding NK and its diagnosis. The new classification allows us to diagnose NK earlier; to accurately monitor progression, evolution, or recurrence; and to assess and evaluate its response to treatment.

Stage 0 is mild (Table 2). Patients have altered sensation without keratopathy; the eye looks completely normal. This is actually the beginning of NK. It's not the persistent epithelial defect, and it's not the ulceration; it's the lack of sensation.

Stage 1 is also mild. The patient has decreased sensation with some epitheliopathy, but the rest of the cornea is healed. There's no haze and no edema. This is the classic case of stain without pain. Patients come in complaining of decreased vision, but they're not complaining about foreign body sensation.

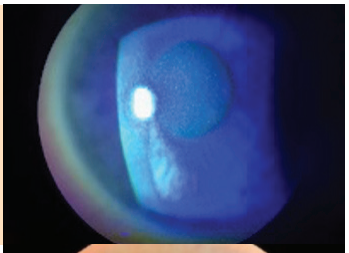
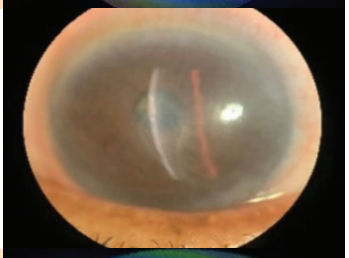
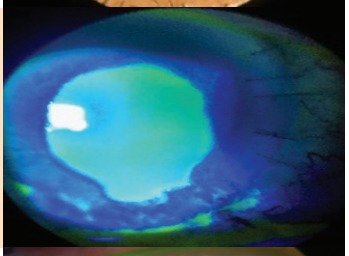
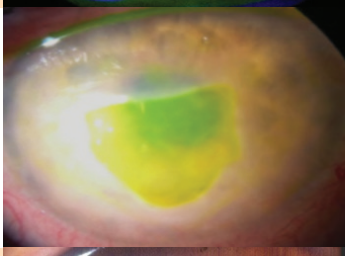
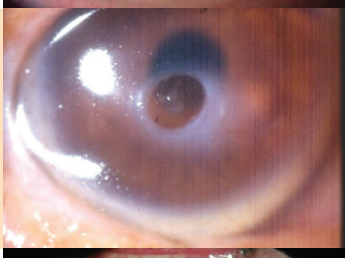
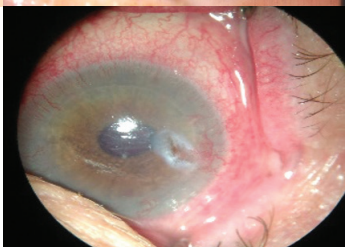
Stage 2 is when we start seeing some stromal haze and a little bit of edema. There is epitheliopathy, but not an epithelial defect. This is moderate disease.

Stage 3 is labeled severe because there is a persistent or recurrent epithelial defects. Ulceration and infection can occur. Some melting of the stroma can also occur and permanent visual morbidity is possible. Within the Mackie classification system, this is considered stage 2 disease.

Stage 4 is also severe. The patient will have persistent or recurrent epithelial defects and stromal scarring without corneal ulceration. In stage 5, which is still severe disease, the patient will have corneal ulceration in addition to persistent and/or recurrent epithelial defects. This is considered stage 3 in the Mackie classification. Stage 6 is corneal perforation, which doesn't need additional description.

We all need to begin thinking of NK earlier. History taking is a key component of patient assessment. You want to rule out some of those causes of impaired trigeminal innervation, which is the

TABLE 2. Neurotrophic Keratitis Study Group Classification
(*submitted for publication*)

STAGE	CLINICAL FEATURES	EXAMPLE
0	Altered sensation without keratopathy	N/A
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	

Images courtesy of Elizabeth Yeu, MD

linchpin of NK. You want to do a complete eye exam. Again, epithelial defects may not be present in NK, and that's when we want to identify it. We want to identify NK before there are epithelial defects, ulcerations, and perforations.

We want to do corneal sensitivity testing, and then we want to do ancillary testing like the Schirmer test and corneal cultures to rule out some of these other issues that may be contributing to NK. Dr. Devries, how do you think about NK?

Dr. Devries: I think about NK much differently now because I used to only think of it in terms of a persistent epithelial defect. I wasn't considering how it started before that. We see post-LASIK patients all the time. We see patients with long-term contact lens use. Many of these patients have decreased corneal sensation. Even if there's no scarring involved, we should be treating it rather than waiting for it to become a persistent corneal defect, which is tougher to heal.

The NKSG classification has dramatically changed my thinking. When I look at patients now and see two or three things clustering together, I feel the need to take a complete case history, formulate a differential diagnosis, and prove it is not neurotrophic related.

Dr. Mah: I use a glaucoma analogy. Are you going to wait until there's vision loss before treating glaucoma? That's essentially what you'd be doing with NK if you wait until there is a persistent epithelial defect or some stromal loss because that can lead to permanent vision loss.

Q | **Dr. Nichols:** In the NKSG staging, how does ulceration present versus a persistent epithelial defect?

Dr. Mah: In the NKSG staging, with an epithelial defect, the rest of the cornea is relatively clear. There is no significant haze or significant edema in the stroma. Some haze or edema may be present, but the Bowman layer remains nice and smooth. If the epithelium heals, then the edema and haze will slowly resolve. Ulceration is when melting of the cornea begins, plus an irregular Bowman layer. If you heal the epithelium, that's obviously great. That's a goal once you've got some ulceration. But there will be some resulting decrease in vision even if the patient heals. It's critical to heal the patient before the ulceration or stromal loss occurs.

SEVERITY-BASED THERAPY FOR NEUROTROPHIC KERATITIS TREATMENT

Dr. Mah: Let's discuss severity-based therapy for NK treatment. In general, we've been taught to start with the preservative-free artificial tears, then progress to ointments and gels, and punctal occlusion. From there, you go to hydrogel contact lenses.[5,6] We also have some relatively newer treatments for persistent epithelial defects for ulceration and NK including serum tears, amniotic membrane, and recombinant human nerve growth factor or cenegermin.

Serum Tears and Plasma Therapy

Dr. Mah: Serum tears or plasma therapy have reported efficacy for NK either as primary or adjunctive therapy. Reported success of serum alone at a concentration of 20 to 50% ranges from 71 to 100% within 90 days.[13-15] That's not bad for persistent epithelial defects ulceration of NK. Although you can get a serum concentration up to 100%, I wouldn't recommend it because it's extremely thick. Umbilical cord serum may be more effective and has higher concentrations of Substance P and nerve growth factor (NGF) than peripheral blood serum.[16] This has led to amniotic extract drops and extra growth factors such as platelet-rich growth factors (PRGF), which is an area of current research. Sanchez-Avila et al found that epithelial defects healed in 97.4% of stage 2 to stage 3 NK after 11 weeks of PRGF.[17] Serum can also be used safely in combination with silicon hydrogel contact lenses; no inflammation or contact lens deposits were observed in a study from Choi et al.[18]

Amniotic Membrane Transplant

Dr. Mah: Next is amniotic membrane transplant (AMT), which is becoming very popular. A randomized clinical trial reported on the healing of refractory neurotrophic ulcers with lubrication plus bandage contact lens or tarsorrhaphy (conventional therapy) compared to AMT.[19] The healing rates were very similar between the two groups (67% with conventional therapy vs 73% with AMT).

It's also fairly equivalent to serum tears in terms of the healing of persistent epithelial defects and NK. A study from Turkoglu et al found that serum tears healed persistent epithelial defects 70% of the time, and AMT healed them 73% of the time.[20] Finally, multilayer AMT is recommended for deep ulcers and descemetoceles. You layer them in the operating room to fill the gap and to make everything level with the rest of the Bowman layer.

Scleral Lenses

Dr. Mah: The use of fluid scleral contact lenses for the treatment of NK was reported decades ago.[21] Ling et al found that nonhealing corneal epithelial defects with bandage contact lenses healed without recurrence in all nine eyes treated with PROSE scleral lens.[22] Sleeping in scleral lenses overnight may accelerate healing as well.[23] Obviously, those patients need very close monitoring.

Corneal Neurotization

Dr. Mah: Corneal neurotization is relatively new; it was first reported in 2014.[24] Corneal sensitivity is restored using a sural nerve graft, which is from the eyelid, and it's joined end-to-end or end-to-side with the supratrochlear nerve. The distal portion of the nerve is separated into different fascicles that are distributed around the limbus of the cornea. It's a very difficult and long multidisciplinary procedure. You need neurosurgeons, an otolaryngologist, and an ophthalmologist. Because of these complexities, it's not very common in the United States, but it does seem to work relatively well.[25,26] One study found that the corneal sensitivity measured pre- and postoperatively with the Cochet–Bonnet, which is again, more of a quantitative measure than aesthesiometer, returned to normal after 5 months.[24] I've heard the efficacy is close to cenegermin or human recombinant NGF. That's very exciting because it may heal and reverse the main issue.

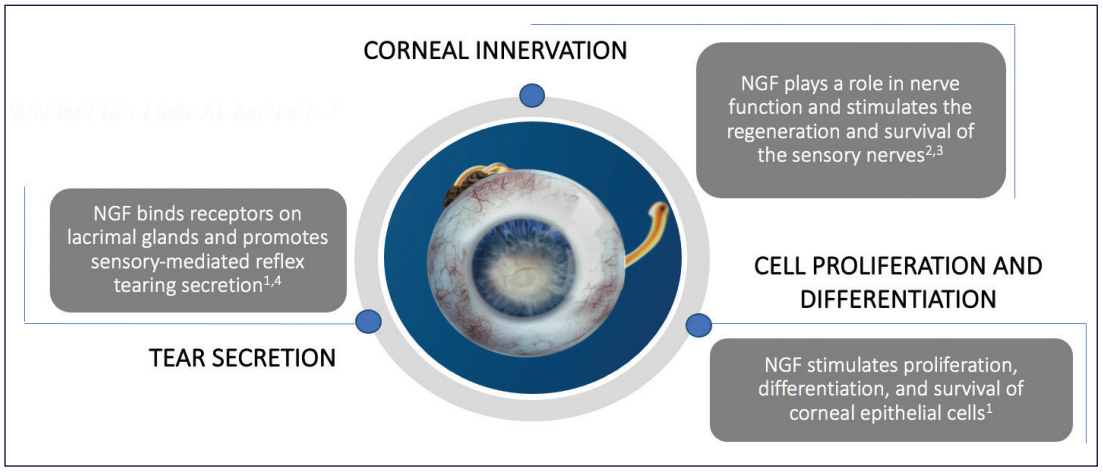


Figure 1. Endogenous NGF maintains corneal integrity by three mechanisms.[4,5,27,28]

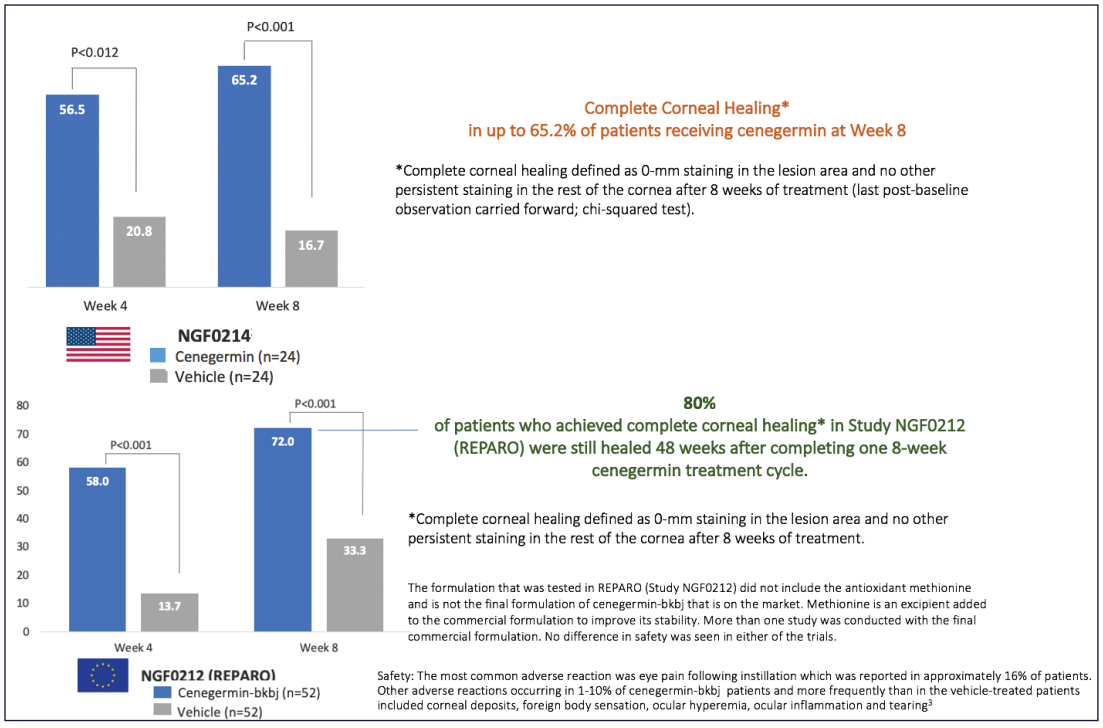


Figure 2. Key efficacy data from cenegermin clinical trials.[31,32]

Dr. Devries: I agree; human recombinant NGF is particularly exciting because it addresses the corneal innervation, which then stimulates the proliferation and differentiation of those cells. It works with tear secretion as well to restore those nerve factors that we have or the nerve going from the cornea back to the brain and back to the tear producing glands (Figure 1).[4,5,27,28] As we look at endogenous NGF and the response we've seen there, it's pretty amazing how fast it works. The active ingredient, cenegermin-bkbj, is structurally identical to human NGF that's produced in the ocular tissue.[29,30] This is what's stimulating those nerve growths in something as fast as an 8-week course. Although this 8-week course is intense, we've had amazing results.

Dr. Nichols: I agree that the results with cenegermin are promising. Many of the treatments we've discussed today are very complicated, requiring referrals and monitoring. They can take months to show results. Cenegermin treatment is much faster. Cenegermin was studied in two 8-week trials: NGF0214, which was conducted in the United States, and NGF0212 (REPARO), which was conducted in Europe.[31,32] The trials were similar. Cenegermin is dosed 6 times a day, 2 hours apart, and requires a fairly consistent approach. Patients administer it themselves as a drop. In the US-based NGF0214 study, 65% of the patients had complete corneal healing at week 8, with a robust response seen as early as week 4 (Figure 2).[31] Complete corneal healing was defined as zero millimeters of staining in the lesion area with no other persistent staining at 8 weeks of treatment.[31,32] This is essentially a cure, which is very difficult to accomplish in this patient group, which had moderate to severe NK.

In REPARO, there were significant *P* values at both 4 and 8 weeks, with 72% experiencing complete corneal healing (Figure 2).[32] Importantly, it was also noted that 1 year after the 8-week treatment cycle, 80% of those who had achieved corneal healing stayed healed. That is remarkable and incredibly encouraging.

Regarding adverse reactions, it shouldn't come as a surprise that 16% of patients on therapy experienced eye pain on installation.[31,32] That is not all that dissimilar from some of the other therapies we put on the ocular surface. Burning and stinging is generally something that happens to eyes that are in poor condition when you start healing them. It's important to note that the reactions were mild and transient and didn't cause anyone to drop out or need additional corrective treatment.

Images courtesy of Marjan Farid, MD

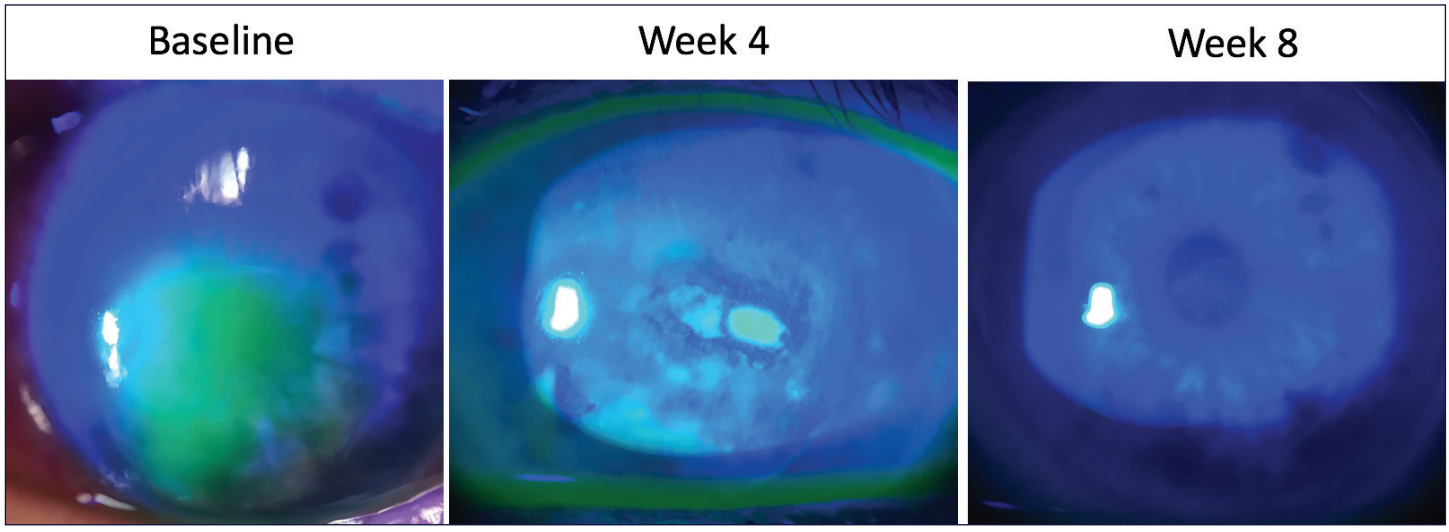


Figure 3. Case 1: Persistent corneal epithelial defect from baseline presentation through week 8 of cenegermin treatment.

The other side effects were very, very mild. Between 1 and 10% of treatment patients experienced some foreign body sensation, ocular hyperemia, ocular inflammation, and tearing.[31,32] Again, those numbers are fairly consistent with what we've seen across other clinical trials. In my mind, this is very good safety data. In summary, 65% of patients with moderate or severe NK who received cenegermin across two clinical studies experienced complete corneal healing. Cenegermin was well tolerated and more effective than vehicle in promoting complete corneal healing. Of those who were healed, 80% of them remained healed for a year.[31,32]

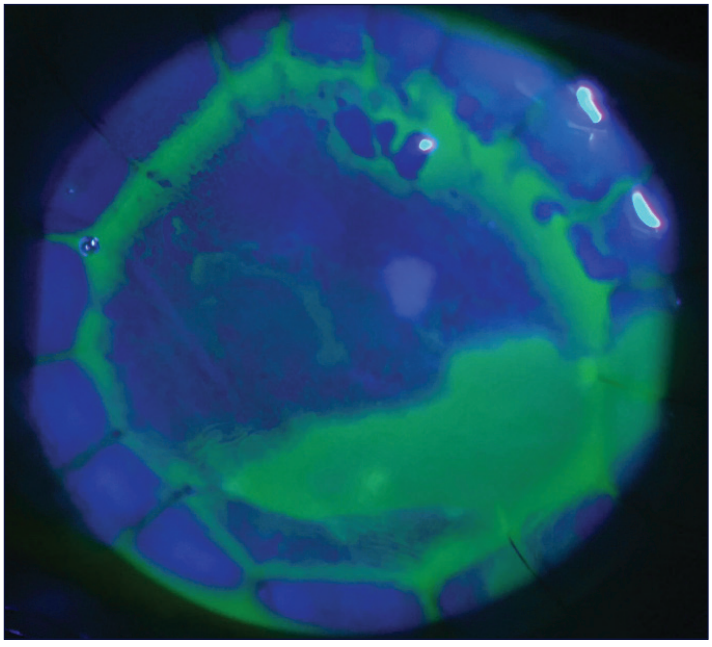
Although dosing 6 times a day every 2 hours may seem aggressive, it's only for 8 weeks. It's actually shorter in duration than the other therapies and treatments we have for NK that are more intensive, require referral, and may not work as well.

CASE 1: PERSISTENT CORNEAL EPITHELIAL DEFECT MANAGED WITH CENEGERMIN

Dr. Devries: Our first case is a 75-year-old man with a 3- to 4-month persistent epithelial defect. He has a history of bilateral LASIK and herpes zoster ophthalmicus which are two significant indications of NK. He also has a previous history of corneal abrasions that healed after 2 weeks with aggressive lubrication. Previous treatments for the epithelial defect include AMT, bandage contact lens therapy, and autologous serum. Concomitant medications include antibiotic drops, artificial tears, and valacyclovir to take care of that viral component. We started the patient on cenegermin for his nonhealing, neurotrophic, corneal epithelial defect. Figure 3 shows the progression from baseline to week 8 of treatment. Healing takes place after week 4, and healing continues to progress until we get that complete corneal healing at week 8.

CASE 2: NEUROTROPHIC KERATITIS IN A PATIENT WITH TYPE 2 DIABETES

Dr. Mah: Our second case is a 45-year-old woman with type 2 diabetes and some peripheral neuropathy. She has proliferative



Images courtesy of Marjan Farid, MD

Figure 4. Case 2: Whirling corneal staining pattern in a patient with 8-week nonhealing cornea epithelial defect.

diabetic retinopathy and had a pars plana vitrectomy for a vitreous hemorrhage. She was referred to me by my retina colleague. She wears contact lenses and is bilaterally pseudophakic. She had a successful vitrectomy, but her vision was reduced. Even with the contact lenses, she wasn't seeing well. The retina colleague treated her for dry eye because she had a lot of corneal staining. The patient tried cyclosporine, lifitegrast, loteprednol, erythromycin ointment, serum tears, and self-retained amniotic membrane and punctal plugs.

When I saw the patient, she was on artificial tears every 1 to 2 hours, omega-3 fatty acids, and also using some warm compresses. If you look at the pattern depicted in Figure 4, it's whirling of the

epithelium. This is not simple dry eye. The patient did not complain too much about pain, just her vision. We did the cotton-wisp test for corneal sensitivity and it was reduced in all quadrants and centrally in both eyes. It's likely caused by the diabetes and the surgeries. I started her on cenegermin on the very first visit. Her vision improved significantly within 2 weeks. At week 4, her VA was about 20/25, and she had a little bit of staining. However, by week 8 her cornea is completely normal; there's no staining. This is very typical for patients, especially those with stage 1 disease. NK is one of those conditions where the earlier you treat, the better the outcome.

Q | **Dr. Nichols:** When you repeat corneal sensitivity testing at week 4 and week 8, do you see a change?

Dr. Mah: That is an excellent question. If you look at the literature, there was an improvement in corneal sensation in the studies, but it was not statistically significant.[31,32] It was a trend they found. I'm finding the same thing; the sensation seems to be better. There are some ongoing studies with confocal imaging, looking at nerves as well, which is even more definitive (personal communication). They are showing what seems to be an increase in the basal nerve plexus of the cornea. I look forward to larger studies looking at corneal sensation and basal nerve plexuses. In general, we should check for corneal sensation after cenegermin treatment. Patients are not only healing, but they are maintaining that ocular surface with only one round of 8-week therapy. That's the impressive component of this drug.

Dr. Nichols: I agree. In working with your patients, how have they responded to the idea of administering drops 6 times a day, 2 hours apart? Have any of you had issues with insurance coverage?

Dr. Devries: I tell patients that it's an intense regimen, and they must be fairly disciplined. In terms of access, it's been incredible. On average, my patients will pay between $50 and $80 for an 8-week supply.

Dr. Mah: I haven't had pushback from patients on the intensity of the regimen. They raise their eyebrows when they hear 6 times a day, every 2 hours, for 8 weeks. But then I explain that 80% of patients maintain their surface afterward with no further treatment. They see the value in that.

Dr. Devries: These patients are frustrated and looking for answers. They appreciate the fact that you have a diagnosis and a treatment.

Q | **Dr. Nichols:** What do you do with the 20% of patients who need additional treatment after the 8-week timeframe? And how do you maintain adherence over time?

Dr. Mah: That's a great question. Not everyone heals after 8 weeks. People do a lot better though, and some people have a smaller epithelial defect at 8 weeks. For the 20% of patients who do not heal, I prescribe a second round of therapy. One patient of mine was completely healed after three rounds of therapy.

As far as maintaining patients, I fall back to preservative-free artificial tears or ointments. I had a patient who works in my billing department who had a rhizotomy due to a trigeminal neuralgia. Unfortunately, the entire right side of her face went numb, including her cornea. We used cenegermin, got her healed, and she's been on preservative-free artificial tears now for 2 years to maintain her ocular surface.

Dr. Nichols: I want to point readers to the cenegermin site because it has a wealth of information for providers on prescribing. It also includes a short video on how to explain the dosing to patients. I recommend you visit the site for additional sources. Thank you to the panel for their thoughtful insights on the diagnosis and treatment of NK. ■

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.
2. Saad S, Abdelmassih Y, Saad R, et al. Neurotrophic keratitis: Frequency, etiologies, clinical management and outcomes. *Ocul Surf*. 2020;18(2):231-236.
3. Dana R, Farid M, Gupta PK, et al. Expert consensus on the identification, diagnosis, and treatment of neurotrophic keratopathy. *BMC Ophthalmol*. 2021;21(1):327.
4. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232(4):717-724.
5. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579.
6. Sheha H, Tighe S, Hashem O, Hayashida Y. Update On cenegermin eye drops in the treatment of neurotrophic keratitis. *Clin Ophthalmol*. 2019;13:1973-1980.
7. Versura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain*. 2018;10:37-45.
8. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15(3):276-283.
9. Yang AY, Chow J, Liu J. Corneal innervation and sensation: the eye and beyond. *Yale J Biol Med* 2018;91(1):13-21.
10. Faulkner W. Corneal diagnostic techniques. *Cornea*. 2010:131-138.
11. Faulkner WJ VG. Cornea: Mosby, 2005.
12. Mackie IA. Current Ocular Therapy: WB Saunders, 1995.
13. Guadilla AM, Balado P, Baeza A, Merino M. [Effectiveness of topical autologous serum treatment in neurotrophic keratopathy]. *Arch Soc Esp Oftalmol*. 2013;88(8):302-306.
14. Jeng BH, Dupps WJ, Jr. Autologous serum 50% eyedrops in the treatment of persistent corneal epithelial defects. *Cornea*. 2009;28(10):1104-1108.
15. Pflugfelder SC. Is autologous serum a tonic for the ailing corneal epithelium? *Am J Ophthalmol*. 2006;142(2):316-317.
16. Yoon KC, You IC, Im SK, et al. Application of umbilical cord serum eyedrops for the treatment of neurotrophic keratitis. *Ophthalmology*. 2007;114(9):1637-1642.
17. Sanchez-Avila RM, Merayo-Lloves J, Riestra AC, et al. Treatment of patients with neurotrophic keratitis stages 2 and 3 with plasma rich in growth factors (PRGF-Endoret) eye-drops. *Int Ophthalmol*. 2018;38(3):1193-1204.
18. Choi JA, Chung SH. Combined application of autologous serum eye drops and silicone hydrogel lenses for the treatment of persistent epithelial defects. *Eye Contact Lens*. 2011;37(6):370-373.
19. Khokhar S, Natung T, Sony P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. *Cornea*. 2005;24(6):654-660.
20. Turkoglu E, Celik E, Alagoz G. A comparison of the efficacy of autologous serum eye drops with amniotic membrane transplantation in neurotrophic keratitis. *Semin Ophthalmol*. 2014;29(3):119-126.
21. Romero-Rangel T, Stavrou P, Cotter J, et al. Gas-permeable scleral contact lens therapy in ocular surface disease. *Am J Ophthalmol*. 2000;130(1):25-32.
22. Ling JD, Gire A, Pflugfelder SC. PROSE therapy used to minimize corneal trauma in patients with corneal epithelial defects. *Am J Ophthalmol*. 2013;155(4):615-9, 9 e1-2.
23. Lim P, Ridges R, Jacobs DS, Rosenthal P. Treatment of persistent corneal epithelial defect with overnight wear of a prosthetic device for the ocular surface. *Am J Ophthalmol*. 2013;156(6):1095-1101.
24. Elbaz U, Bains R, Zuker RM, et al. Restoration of corneal sensation with regional nerve transfers and nerve grafts: a new approach to a difficult problem. *JAMA Ophthalmol*. 2014;132(11):1289-1295.
25. Terzis JK, Dryer MM, Bodner BI. Corneal neurotization: a novel technique for the anesthetic cornea. *Cornea*. 2010;29(7):812-819.
26. Liu CY, Arteaga AC, Fung SE, et al. Corneal neurotization for neurotrophic keratopathy: Review of surgical techniques and outcomes. *Ocul Surf*. 2021;20:163-172.
27. Muller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res*. 2003;76(5):521-542.
28. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29(10):1163-1168.
29. Lambiase A, Rama P, Bonini S, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med*. 1998;338(17):1174-1180.
30. Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320(13):1309.
31. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal trial. *Ophthalmology*. 2020;127(1):14-26.
32. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology*. 2018;125(9):1332-1343.
33. Mackie IA. Neuroparalytic keratitis. In: Roy FH, Meyer SM, Fraunfelder FT, eds. *Current Ocular Therapy*. Philadelphia, PA: W. B. Saunders, 1995.

NEUROTROPHIC KERATITIS: THE LATEST APPROACHES IN DIAGNOSIS, CLASSIFICATION, AND TREATMENT

Release Date: Jan. 7, 2022
COPE Expiration Date: Jan. 6, 2024

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, go to http://evolvemeded.com/course/2151-supp. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

Please type or print clearly, or we will be unable to issue your certificate.

Full Name_____ DOB (MM/DD): _____

Phone (required) _____ Email (required*) _____

Address/P.O. Box_____

City _____ State/Country _____ Zip _____

License Number:_____OE Tracker Number:_____National Provider ID:_____

*Evolve does not share email addresses with third parties.

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week
(with the disease targeted
in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Describe the stages of neurotrophic keratitis, and how to differentiate it from similar diseases	_____	_____	_____
Recognize the various potential causes of neurotrophic keratitis and when referrals may be necessary	_____	_____	_____
Summarize mechanisms of action of newer treatments and when they should be introduced into treatment regimens for neurotrophic keratitis	_____	_____	_____
Identify the relationships between disease characteristics, drug, treatment frequency, visual and anatomic outcomes	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to describe the mechanisms of action of newer treatments and when they should be introduced into treatment regimens for 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. Ms. Smith is referred into your clinic for a dry eye evaluation. She has a history of type 2 diabetes, proliferative diabetic retinopathy, and bacterial corneal ulcers with poor healing that required penetrating keratoplasty; 2 months later the epithelium has not yet healed. Previous treatments included antibiotics, steroids, bandage contact lenses, and self-retaining amniotic membrane. Corneal sensitivity testing reveals centrally absent sensation. What would be considered an appropriate next step?

a. Continue with biologic corneal bandage
b. Increase steroid-free artificial tears to 5 times daily
c. Initiate a 6-week course of cenegermin 8 times daily
d. Initiate an 8-week course of cenegermin 6 times daily

3. _____ is a hallmark clinical test to diagnose NK.

a. Visual acuity testing
b. In vivo confocal microscopy
c. Corneal sensation testing
d. Imaging with a slit lamp

4. Corneal innervation is essential for good epithelial health. How do corneal nerves maintain a healthy corneal surface?

a. Provide stromal, epithelial, and Bowman's structural support
b. Maintain sensory functions that are essential to tear film maintenance
c. Facilitate protective functions of blinking and tear production as well as trophic support
d. Provide key nutrients to the epithelium while also serving as a physical barrier to microbes

5. Endogenous nerve growth factor helps preserve and restore the ocular surface by which of the following mechanisms?

a. Strengthening tight junctions between epithelial cells to enhance corneal epithelial barrier functions.
b. Providing nutrition to conjunctival goblet cells and eyelid tear glands in order to increase tear production and improve tear quality.
c. Stimulating limbal stem cells to generate new epithelial cells.
d. Increasing tear production at the lacrimal gland, stimulating nerve regeneration, and supporting epithelial cell proliferation and differentiation.

6. NK results from damage to which of the following nerves?

a. Oculomotor Nerve (CN III)
b. Trochlear Nerve (CN IV)
c. Trigeminal Nerve (CN V)
d. Abducens Nerve (CN VI)
e. Facial nerve (CN VII)

7. Rank in order from greatest to least the areas of highest corneal sensation:

a. Inferior limbus> temporal limbus> central cornea
b. Temporal limbus> central cornea> inferior limbus
c. Central cornea> temporal limbus > inferior limbus
d. Central cornea> inferior limbus > temporal limbus

8. Which of the following steps should be utilized while performing corneal sensitivity testing?

a. Check both eyes
b. Test in the center and all four quadrants of the cornea
c. Apply topical tetracaine first, then check sensitivity
d. All of the above
e. A+B

9. What treatment options are available for NK?

a. Amniotic membrane
b. Autologous serum tears
c. Scleral lenses
d. Cenegermin
e. All of the above

10. What was the most common adverse event seen in clinical trials with cenegermin?

a. Foreign body sensation
b. Eye pain on instillation
c. Ocular Inflammation
d. Tearing
e. Corneal deposits

11. In the European cenegerimin trial, what percentage of patients who healed after one 8-week course of treatment remained healed at 1 year?

a. 70%
b. 75%
c. 80%
d. 85%

12. Complete corneal healing, defined as 0 mm staining in the lesion area and no other persistent staining in the rest of the cornea after 8 weeks of treatment, was achieved in what percentage of patients receiving cenegermin in the European Trial?

a. 45%
b. 55%
c. 65%
d. 75%

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 participating in this course: 5 = High, 1 = Low_____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low_____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____No

Probability of changing practice behavior based on this activity: _____High _____ Low _____No change needed

If you plan to change your practice behavior, what 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 that 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 content conveyed	___ Yes	___ No
The content supported the identified learning objectives	___ Yes	___ No
The content was free of commercial bias	___ Yes	___ No
The content was relative to your practice	___ Yes	___ No
The faculty was effective	___ Yes	___ No
You were satisfied overall with the activity	___ Yes	___ No
Would you 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
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this activity; may we contact you by email in 3 months to see if you have made changes as a result of this activity? If so, please provide your email address below.

_____

_____