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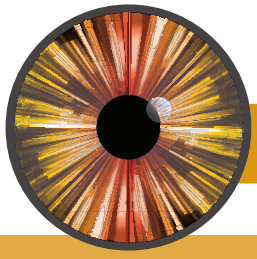
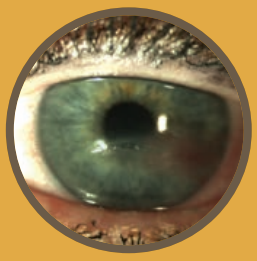
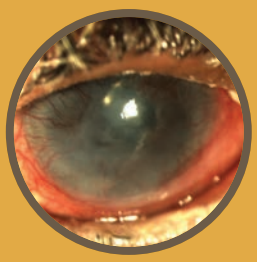
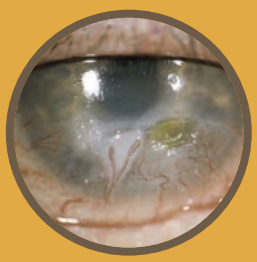


CLINICAL CONSULTATIONS™ IN NEUROTROPHIC KERATITIS







FACULTY

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Activity Description and Purpose

Neurotrophic keratitis is a rare but potentially sight-threatening corneal degenerative disease. Early recognition of neurotrophic keratitis is important to allow appropriate treatment that will promote corneal healing and prevent progression to more extensive, permanent corneal destruction. The content of this activity is based on the proceedings of a live CME symposium that covered the pathogenesis of neurotrophic keratitis, diagnostic evaluations, and strategies for management through reviews of the literature and clinical data, discussions among corneal experts, and detailed case histories of patients with varying stages of neurotrophic keratitis.

Target Audience

This educational activity is intended for ophthalmologists.

Learning Objectives

After completing this activity, participants will be better able to:

- Describe the role of corneal sensory innervation in ocular surface health
- Integrate evaluation of corneal sensitivity into assessment of ocular surface disease
- Interpret evidence of corneal healing and reinnervation in patients treated with recombinant human nerve growth factor
- Select treatment strategies for patients diagnosed with any stage of neurotrophic keratitis

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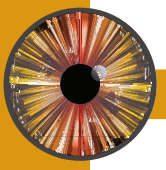

CLINICAL CONSULTATIONS™ IN NEUROTROPHIC KERATITIS

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Introduction

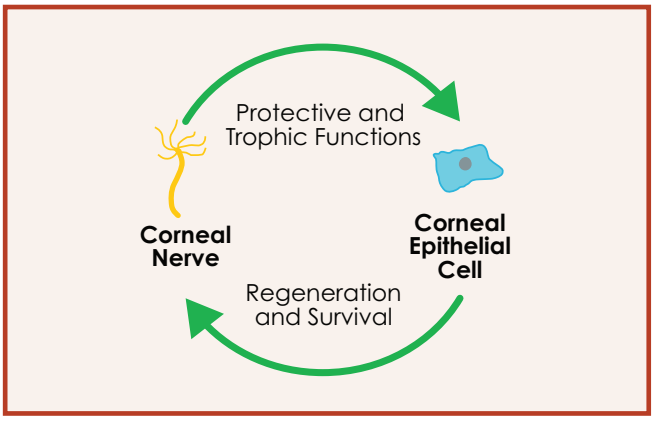
Neurotrophic keratitis (NK) is a rare but potentially sight-threatening corneal degenerative disease. Early recognition of NK is important to allow appropriate treatment that will promote corneal healing and prevent progression to more extensive, permanent corneal destruction. The diagnosis of NK in eyes with early-stage disease, however, is often overlooked.

In this educational activity, cornea specialists will review the pathogenesis of NK, along with elements of the diagnostic evaluation and strategies for management. Detailed case histories involving patients representing the spectrum of NK severity, accompanied by expert discussions, will further illustrate clinical considerations for detecting NK and selecting appropriate treatment.

Definition, Prevalence, Pathogenesis, and Etiology

Neurotrophic keratitis is a degenerative corneal disease caused by damage to the trigeminal nerve (cranial nerve V) that leads to loss of corneal sensation, corneal epithelial breakdown, and impaired healing, with risk for epitheliopathy progression to a persistent epithelial defect (PED), corneal ulceration, stromal melting, and perforation.[1] Neurotrophic keratitis has been considered a rare/orphan disease on the basis of an estimated prevalence of < 0.016% (< 1.6/10,000 persons), which was derived through extrapolation of data on the percentage of patients who develop NK in association with its 2 most common causes (herpetic keratitis and postsurgical nerve damage).[2,3] It is believed, however, that many cases of NK are overlooked, and more recent retrospective epidemiologic data suggest that its prevalence is 0.11% (11/10,000 persons).[3]

The pathogenesis of NK is explained by understanding that the corneal nerves and corneal epithelial cells are involved in a mutually supportive relationship, so corneal nerve impairment initiates a vicious cycle that perpetuates progression of neuronal and epithelial damage **(Figure 1)**.[2-6] Corneal nerves maintain corneal integrity by stimulating protective blinking and tearing, and are also a source of neuropeptides that provide trophic support and mediate wound healing. Corneal epithelial cells support corneal nerves by producing neurotrophic factors, such as nerve growth factor, which promote neuronal extension and survival.



// **FIGURE 1** / Corneal nerves and corneal epithelial cells act in a mutually supportive relationship.[2-6] Corneal nerve damage leads to corneal epithelial damage, which initiates a vicious cycle that perpetuates progression of neuronal and epithelial damage.

Multiple etiologies can impair trigeminal nerve function and underlie NK.[2,7] In addition to herpetic infections and surgically induced nerve damage, the list of underlying causes include various ocular, systemic, central nervous system, and genetic conditions **(Table 1)**.[2,7]

// **TABLE 1** / Neurotrophic Keratitis Etiologies[2,7]

Ocular	Systemic
• Herpes simplex/zoster • Chronic keratoconjunctivitis sicca • Long-term contact lens wear • Penetrating and deep lamellar keratoplasty • Corneal refractive surgical procedures • Corneal dystrophies • Limbal stem cell deficiency • Topical drug toxicity • Chemical injury	• Diabetes • Multiple sclerosis **Central nervous system** • Brainstem neurosurgery • Cerebrovascular accident • Degenerative disorders • Tumors **Genetic** • Riley-Day syndrome • Mobius syndrome

Diagnosis

The diagnosis of NK is based mainly on a clinical history of a condition associated with trigeminal nerve impairment, combined with the presence of corneal epitheliopathy, PEDs, or ulcers and decreased corneal sensitivity.[7] Clinicians who suspect NK according to the patient's history and/or clinical features should test for loss of corneal sensitivity, which is the diagnostic hallmark for NK. If corneal sensitivity is reduced, additional evaluations will provide information for differential diagnosis and staging and determine the etiology of the NK if it was not already apparent.

Discussion

Dr Donaldson: Assessment of corneal sensation is essential to diagnosing NK and should always be done before any anesthetic drops are administered. Corneal sensation can be easily tested by noting the patient's reaction when a cotton wisp or a piece of dental floss touches the cornea, or it can measured with a Cochet-Bonnet esthesiometer.[2] The Belmonte gas esthesiometer is a noncontact device that can also be used, but it is not widely available.

Although I have access to a Cochet-Bonnet esthesiometer, for convenience I generally test corneal sensitivity with a cotton wisp, which is on hand in every examination room. What do you use?

Dr Rapuano: I also use a cotton wisp.

Dr Pflugfelder: Our clinic also has a Cochet-Bonnet esthesiometer, but I have been using dental floss.

Dr Donaldson: How often do you assess corneal sensation? I expect we test more patients than do most ophthalmologists because we are cornea specialists in tertiary care practices. I think, however, that even in a general ophthalmology practice, these patients are more common than once appreciated.

Dr Rapuano: I test corneal sensation fairly frequently. In particular, I test any patient with epitheliopathy associated with chronic ocular surface disease. If the patient has NK, I want to diagnose it before progression to a chronic epithelial defect that can rapidly advance to more extensive involvement. Longstanding diabetes is another red flag for me, and there are many patients with this history.

Dr Pflugfelder: I also test cornea sensation in any patient with significant epitheliopathy.

Dr Donaldson: Some cosmetic procedures, such as blepharoplasty or facelift, can lead to trigeminal nerve damage, but patients are not always forthcoming about that history. Therefore, I make it a point to ask specifically about these surgical procedures.

Dr Rapuano: I find that some patients fail to mention a history of corneal refractive surgery.

Dr Donaldson: That is my experience as well. It seems some people do not consider LASIK (laser-assisted in situ keratomileusis) to be a surgical procedure.

Staging

Historically, the severity of NK has been described using the Mackie classification system, which divides the condition into 3 stages according to clinical features[2,8]:

- **Stage 1:** Punctate epitheliopathy (punctate corneal fluorescein/lissamine green staining), decreased tear breakup time, and stromal haze
- **Stage 2:** PED with smooth rolled edges and stromal opacity
- **Stage 3:** Stromal thinning/ulceration and corneal perforation

It is believed, however, that the diagnosis of early NK is often overlooked because of overlap between the defining features of stage 1 NK and dry eye disease (DED). Because recognition of NK at an early stage is important for allowing intervention that can prevent progression to more severe corneal damage, the American Society of Cataract and Refractive Surgery (ASCRS) Neurotrophic Keratitis Study Group proposed an expanded staging scheme to encourage earlier diagnosis and treatment **(Table 2)**.[9] The new staging scheme, which recognizes a range of disease severity within each of the 3 Mackie stages, divides NK into 7 stages numbered from 0 to 6.

// **TABLE 2** / ASCRS Neurotrophic Keratitis Study Group Proposed Staging Scheme[9]

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

Abbreviation: ASCRS; American Society of Cataract and Refractive Surgery.

Discussion

Dr Pflugfelder: Do you think the Mackie classification system limits the ability of clinicians to identify NK?

Dr Donaldson: I think that the simplicity of the Mackie system really enables NK detection by comprehensive ophthalmologists, whereas the more refined ASCRS staging scheme is useful for specialists, for more complex cases, and for stratifying patients in research studies.

Dr Rapuano: I agree. For example, Mackie stage 3 describes any eye with stromal tissue loss, but there is a huge difference between eyes with 1% tissue loss and those with a perforation.[8] In clinical studies, it is helpful to stage patients using the ASCRS system, which divides them according to the extent of loss.[9] For general ophthalmologists involved in patient care, however, it is enough to recognize the presence of any stromal thinning, which represents an emergent situation.

Dr Pflugfelder: I also like the simplicity of the Mackie system for use by general ophthalmologists, but I think that the ASCRS scheme offers value to them as well because it divides cases with corneal epitheliopathy according to the absence or presence of stromal involvement.[9] It is important that clinicians recognize and treat NK before stromal haze develops because it can permanently affect vision. Are there any key features of the expanded classification that influence your treatment?

Dr Rapuano: The identification of stromal haze is a sign to step up treatment intensity. The division based on absence or presence of ulceration (stage 4 vs stage 5) is also important because, as I said, there is a big distinction between eyes with minimal tissue loss, 1% or 5%, and those with 95% loss.[9]

Treatment of Neurotrophic Keratitis

Treatment of NK aims to promote corneal epithelial healing and to prevent disease progression. Many topical, systemic, surgical, and nonsurgical procedural modalities are used to treat NK; they are implemented in a severity-based stepladder approach together with interventions targeting any modifiable underlying conditions.[2,5,10] Treatments for NK are briefly described subsequently. The following section, which presents a series of case histories, illustrates their application in clinical care.

Medical Management

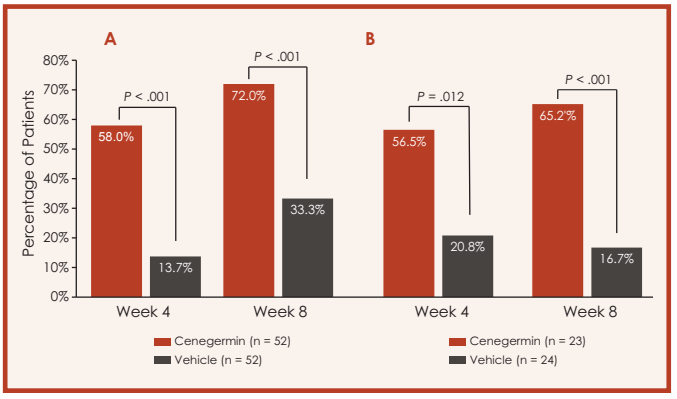
Universal medical management of NK incorporates significant lubrication with preservative-free artificial tear formulations and other modalities, as appropriate to treat DED and optimize the ocular surface.[2] Inflammation associated with DED may be clinically apparent or its presence can be confirmed using the matrix metalloproteinase-9 assay. A tapered course of a topical steroid can treat active inflammation if there is not an infiltrate. Topical cyclosporine A or lifitegrast can be started as chronic therapy to control DED-related inflammation. Oral doxycycline has anti-inflammatory activity and inhibits matrix metalloproteinases.[11] It has been reported to improve or accelerate epithelial healing and is a good choice for patients with comorbid ocular rosacea.

For all patients with NK, existing topical medications should be reviewed with an aim to eliminate offending drops.[2] Instructing patients to bring all their medications to the visit is helpful because the self-reported history may be incomplete. Topical nonsteroidal anti-inflammatory drugs, in particular, should be stopped because they have been associated with corneal melts.[12] Medications for intraocular pressure (IOP) lowering that contain a preservative can be switched to a preservative-free alternative or an oral medication.[2] Alternatively, earlier surgery can be considered to eliminate or reduce the need for medical IOP-lowering treatment.

A topical broad-spectrum antimicrobial agent should be started to prevent infection in eyes with an epithelial defect.[2,13] Moxifloxacin can be a good choice because it is self-preserved, and it may be instilled just once or twice a day when used for prophylaxis.[14] Antiviral treatment may be started in patients with a history of herpetic keratitis.

Topical blood-derived products (serum tears, platelet-rich plasma, plasma rich in growth factors [PRGF]) contain growth factors and proteins that can serve as a substrate for epithelial growth and promote healing.[2,7] Topical cenegermin ophthalmic solution, 0.002% (recombinant human nerve growth factor), which is the only medication approved by the US Food and Drug Administration (FDA) for the treatment of NK, can be considered to treat any stage of the disease.[15]

The safety and efficacy of cenegermin were established in 2 prospective vehicle-controlled trials; one was conducted in Europe and the other in the United States.[16,17] Both studies enrolled patients with Mackie stage 2 and 3 NK and randomly assigned them to receive treatment with cenegermin (n = 52 in the European study; n = 24 in the US study) or vehicle (n = 52 in the European study; n = 24 in the US study) 6 times a day for 8 weeks. The rate of complete corneal healing (0.0-mm staining in the lesion area and no other persistent staining in the rest of the cornea) at 8 weeks was significantly higher in the cenegermin group than in the control group in both the European (72.0% vs 33.3%, respectively) and US studies (65.2% vs 16.7%, respectively) ($P < .001$ for both comparisons); a statistically significant difference favoring cenegermin was also observed at week 4 in both trials **(Figure 2)**. A pooled post hoc analysis evaluating change from baseline lesion size among patients who did not meet the complete corneal healing end point also showed a significant difference favoring cenegermin over vehicle (-36.3% vs +46.8%; $P = .021$).[18] Corneal sensitivity improved in all study groups; the change was greater in the cenegermin group in both trials, but the difference compared with vehicle was not statistically significant.[16,17]



// **FIGURE 2** / Percentages of patients achieving complete corneal healing in the European (A) and US (B) cenegermin trials[16,17]

In a pooled data safety analysis, eye pain was the most common adverse event in both the cenegermin (n = 75) and vehicle (n = 76) groups (16% vs 8%, respectively).[19] The only other adverse events occurring at a rate of ≥ 5% were ocular hyperemia (7% with cenegermin and 3% with vehicle) and increased lacrimation (5% with cenegermin and 3% with vehicle).

Discussion

Dr Rapuano: In my experience, approximately 20% to 25% of patients using cenegermin experience eye pain. It tends to develop 2 to 3 weeks after starting treatment and lasts for 1 or 2 weeks. I warn patients about the pain and tell them it is a good sign because it means their nerves are working. The pain can be significant, and I sometimes decrease cenegermin dosing from 6 times a day to 3 or 4 times a day until the pain improves, which can happen in a few days or take up to 2 weeks.

Dr Donaldson: I think most patients begin to feel pain as their corneal sensation improves, which might be as early as after 1 week. Patients who have been wearing a bandage contact lens (BCL) may have more issues with pain because the BCL is removed when they start cenegermin. I also warn patients to expect pain, and I instruct them to increase the frequency of the preservative-free lubricant if it occurs. I may also increase steroid dosing temporarily. For example, I may use loteprednol or preservative-free methylprednisolone once or twice daily to ease any return of sensation during treatment.

Dr Pflugfelder: Do you recommend patients use vitamin C? I tell patients to use it at high doses in cases of burns. I also recommend an oral omega-3/omega-6 supplement.

Dr Donaldson: I also recommend omega supplementation and vitamin C because vitamin C has been shown to promote corneal epithelial healing.[20]

Dr Rapuano: I recommend vitamin C and doxycycline whenever there is more than 10% stromal thinning.

Surgical and Other Nondrug Interventions for Neurotrophic Keratitis

A dry environment can exacerbate NK, so humidification can be helpful.[2] Punctal plugs can enable healing by increasing tear retention, but should not be used if there is uncontrolled inflammation. Punctal cautery occlusion can be considered if the plugs are not providing sufficient benefit.

A BCL provides comfort and protection.[2] Other modalities for ocular surface protection include botulinum neurotoxin injection to induce ptosis, tarsorrhaphy, and a scleral lens. A scleral lens also improves visual acuity,[21] and its reservoir can be filled with a blood-derived product that will promote healing. Surgery to create a conjunctival flap can be very effective for promoting healing of a chronic epithelial neurotrophic defect, but compromises vision and cosmesis.[22]

Amniotic membrane transplantation (AMT) protects the ocular surface and promotes healing by providing a substrate for epithelial cell migration and attachment, along with a host of molecules that are critical for healing and inflammation control.[2,23] Forms of amniotic membrane that are marketed in the United States include cryopreserved self-retaining sheets that can be applied in the office and freeze-dried products that require rehydration but have a longer shelf life. Amniotic membrane is also available as a homogenate eye drop, although products in this category are not FDA approved.

Tissue adhesives or glue are used if there is severe thinning or perforation, but keratoplasty is urgently needed if the cornea is perforated.[2] Surgical neurotization to restore trigeminal nerve function is another surgical option.

Discussion

Dr Rapuano: My preference for AMT is to use the cryopreserved self-retaining product because it stays on the eye. Freeze-dried AMT is easy to apply and is then covered with a BCL, but it can be hard to tell if the AMT is still on the eye after a day or 2, which makes me wonder if any benefit I see is from the BCL alone.

Dr Pflugfelder: What are your thoughts on surgical neurotization?

Dr Rapuano: I have no personal experience with it, but it seems to be gaining traction in the United States. It can be done with a direct or interpositional autologous nerve graft or with an acellular nerve allograft.[24] Reported results show that it is effective for restoring sensation, but it takes months to see the benefit.[24]

Dr Pflugfelder: A former colleague of mine is treating patients with neurotization followed by cenegermin. I used that approach for 1 patient. I collaborated with a plastic surgeon colleague who did the surgical procedure, and I was impressed with the patient's outcome.

What is the role of stem cell transplantation in NK?

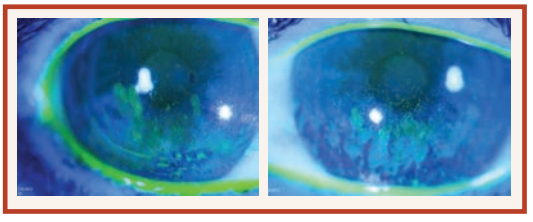
Dr Donaldson: I think it depends on the etiology of the NK, but it could be helpful in a patient with limbal stem cell deficiency who has not responded to medical treatment of NK.

Clinical Case Discussions: The Stepladder Approach to Treatment for Neurotrophic Keratitis

Case 1: Post-LASIK Patient With Fluctuating Vision

From the Files of Kendall E. Donaldson, MD, MS

A 65-year-old woman with a history of LASIK presented with concerns about blurry fluctuating vision. She had worn rigid gas permeable contact lenses for 40 years before LASIK and had a history of scleroderma. She denied having symptoms of foreign body sensation, redness, burning, or pain.



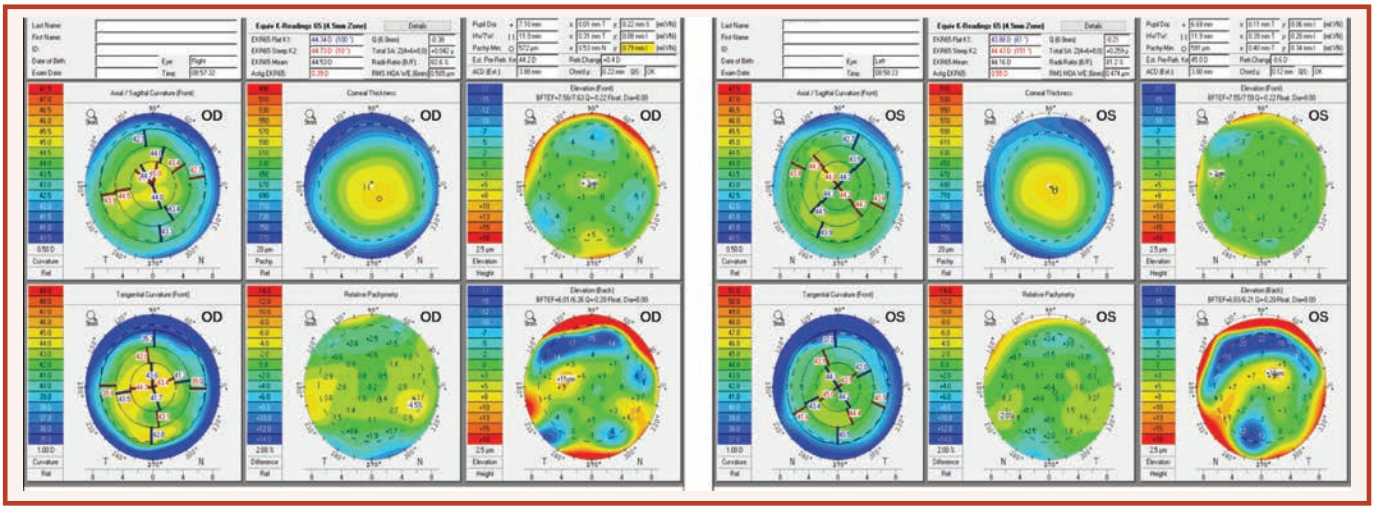
// **FIGURE 3** / Diffuse epitheliopathy overlying the laser-assisted in situ keratomileusis flaps of the patient in Case 1

Best-corrected visual acuity was 20/30 OD and 20/25 OS. Examination showed dermatochalasis, 2+ meibomian gland dysfunction OU, mild nasal pinguecula OU, LASIK flaps, and 2+ punctate epithelial erosions OU (Figure 3). Anterior chambers were deep and quiet; iris was within normal limits with good dilation; early cataract (1+ nuclear sclerotic, 1+ cortical) was present OU; and cup-to-disc ratios were 0.55/0.5 OD/OS. Corneal sensitivity was tested with a cotton wisp and was diminished OU. Dry eye evaluation showed osmolarity 304/319 mOsm/L OD/OS; positive MMP-9 OU; 1+ lid margin staining; 2+ punctate epithelial erosions; and foamy secretions OU. Figure 4 shows maps from topography.

Dr Donaldson: This patient had multiple findings that raise suspicion for NK, including moderate punctate epitheliopathy and a history of both prior LASIK and long-term contact lens wear. I think that all patients have some NK after undergoing a corneal refractive procedure. The nerves regenerate over time, but there may be some persistent changes.

Patients with NK secondary to herpes infection may have only 1 affected eye, so the fellow eye can be used for comparison when testing for reduced corneal sensitivity. It can be a little trickier to diagnose NK in a case such as this, in which the findings are more symmetric because the NK is related to previous bilateral surgery. The same is true when the etiology is a systemic disease.

This case also highlights the need to maintain an index of suspicion for NK in patients who present with significant epitheliopathy, especially when the patient presents, as this woman did, without any symptoms. Findings from a few studies show that DED is common in patients who present for cataract surgery and is often asymptomatic.[25,26] Then, in patients with early cataract, it can be challenging to determine if the visual dysfunction is related to the lens or to the cornea. The answer is important because it determines the need for cataract surgery, and it also affects intraocular lens selection. When such conditions are identified preoperatively, they can be addressed with the patient and treated in order to get the most accurate lens measurements in preparation for cataract surgery. In some



// **FIGURE 4** / Surface irregularities of the patient in Case 1 noted on topography

more severe cases, a presbyopia-correcting intraocular lens may not be an appropriate choice for a patient with NK or other forms of moderate to severe ocular surface disease.

I find that ray tracing aberrometry is helpful in distinguishing if visual dysfunction is from the cataract or from the cornea. In addition, I always get corneal topography in the preoperative evaluation of patients having cataract surgery. I think that many cataract surgeons are using corneal tomography because it gives information on the posterior cornea, but looking at the Placido rings on corneal topography is very helpful for picking up ocular surface issues.

Dr Rapuano: Explaining to patients that the distorted rings on their Placido topography image show that the cornea is very unhealthy can motivate them to be compliant with recommended treatment. Then, it can be hard to decide when the patient is ready for cataract surgery. Ideally, we would like a perfect ocular surface, but that might never happen.

The patient was diagnosed with Mackie 1, ASCRS 1 NK according to the presence of corneal epitheliopathy without stromal involvement. She was treated with preservative-free artificial tears every 2 hours and ointment at night, loteprednol 4 times daily and tapered over 2 months, lifitegrast twice daily, and serum tears. The ocular surface improved (Figure 5), and the patient went on to have cataract surgery.

Dr Donaldson: The therapeutic goals for Mackie stage 1 NK are to prevent epithelial breakdown, improve epithelial quality, and prevent progression.[2,6,10] This is done by using preservative-free ocular lubricants, eliminating offending agents, and managing underlying etiologies; cenegermin and punctal occlusion are also options to consider to promote healing and increase ocular surface lubrication **(Table 3)**.

// **TABLE 3** / Treatments for Mackie Stage 1 Neurotrophic Keratitis[2,6,10]

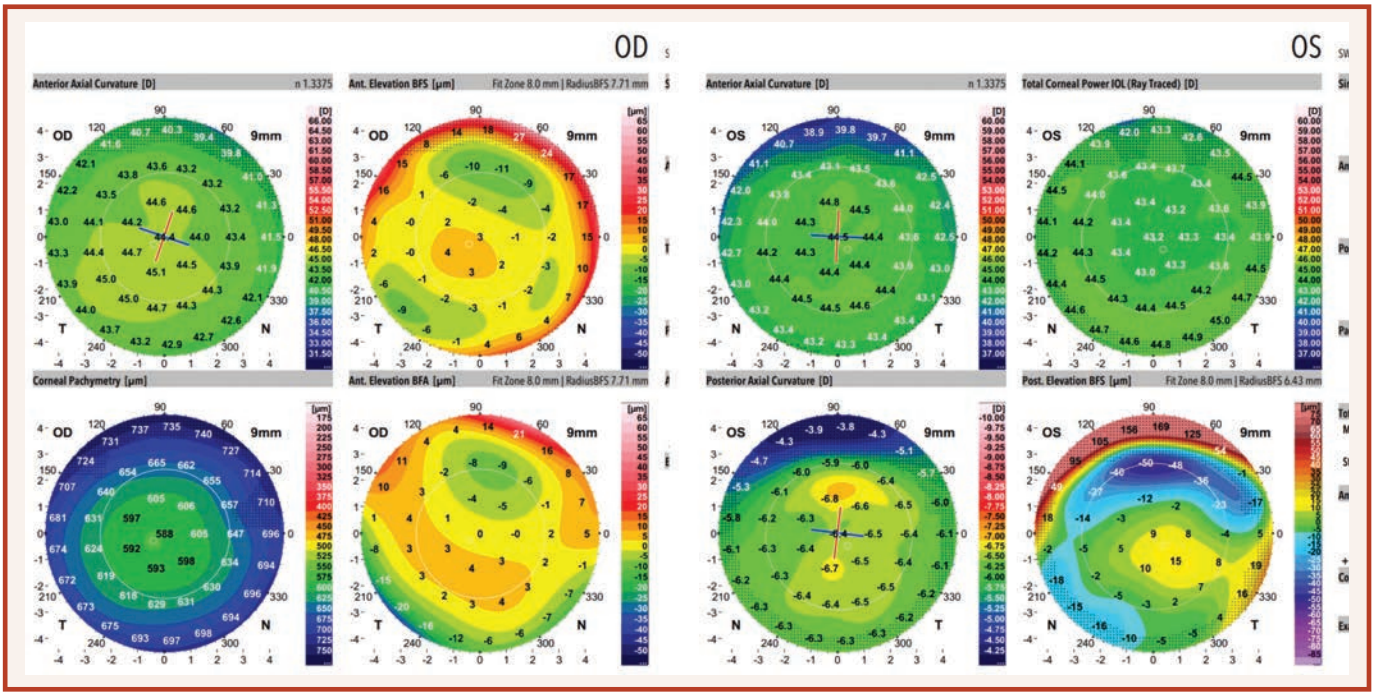
Preservative-free ocular lubricants
Punctal occlusion (only if inflammation is controlled)
Discontinue topical medications, especially products containing preservatives or toxic active ingredients
Cenegermin
Treat existing inflammation and ocular surface disease
• Anti-inflammatory agents (corticosteroids, lifitegrast, cyclosporine)
• Doxycycline
• Omega fatty acid supplementation
Treat other underlying etiologies (eg, herpetic infection, lid abnormalities)

Case 2: Patient With a Nonhealing Epithelial Defect

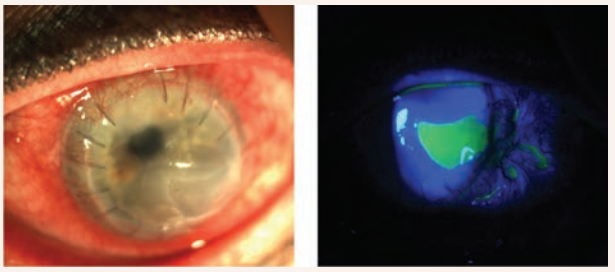
From the Files of Stephen C. Pflugfelder, MD

A 65-year-old woman was seen on referral for a nonhealing corneal epithelial defect in her left eye that developed after she had a second penetrating keratoplasty for pseudophakic edema. The patient had type 1 diabetes and had a retinal detachment in her other eye.

On presentation, her vision was count fingers at 5 ft in the left eye. There was stromal edema, haze, and vascularization in the area of the epithelial defect, along with surrounding punctate epitheliopathy (Figure 6). The corneal endothelium was normal. Corneal sensitivity was poor (Cochet-Bonnet esthesiometer measurement of 1 mm); Schirmer 1 score was 8 mm; and the blink rate was reduced. The patient had been on prednisolone acetate 4 times daily and latanoprost, 0.005%, at bedtime. She was diagnosed with Mackie 2 (presence of PED),



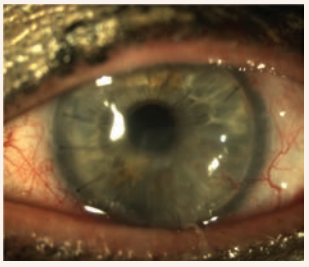
// **FIGURE 5** / Improvements in surface irregularities of the patient in Case 1 noted on corneal topography



// **FIGURE 6** / Appearance of left cornea of the patient in Case 2 at presentation with a nonhealing epithelial defect on the corneal graft

ASCRS 4 (PED with stromal scarring, edema, haze, and vascularization, but no ulceration) NK. The patient was treated with preservative-free dexamethasone, 0.1%, switched to oral methazolamide 50 mg twice daily for IOP control, and started on topical PRGF. Soon, however, she was fitted with a scleral contact lens with PRGF in the reservoir.

The epithelium healed within 1 month. At 10 months, the stromal opacity and vascularization were decreased (Figure 7). Visual acuity improved to 20/60.



// **FIGURE 7** / Appearance of left cornea of the patient in Case 2 after 10 months of therapy

Dr Pflugfelder: Therapeutic options for Mackie stage 2 NK include treatments for DED and avoidance of topical treatments that can worsen the condition **(Table 4)**.[2] Additional modalities for providing corneal protection include a BCL, scleral lens, tarsorrhaphy, and an amniotic membrane graft that also promotes healing. Treatment with cenegermin and a blood-derived product are also appropriate to stimulate healing. In case of an inadequate response, the blood-derived product can be put in the reservoir of a scleral lens. It is not yet known if cenegermin can also be used in that manner. Other options include an amniotic membrane graft, botulinum neurotoxin–induced ptosis, and then tarsorrhaphy if all else fails.

// **TABLE 4** / Treatment of Mackie Stage 2 Neurotrophic Keratitis[2]

All stage 1 strategies, plus:

- Bandage contact lens
- Autologous blood-derived tear products
- Scleral lens (± serum/plasma)
- Amniotic membrane graft
- Tarsorrhaphy

I use a hydrogel BCL initially in almost all patients with NK to decrease exposure and to promote epithelial healing. A recent report described the use of cenegermin with a BCL.[27] Although I tend not to use them together, I have tried it in a few patients.

As was done with this patient, I use a scleral lens in nonresponsive cases. By creating a new environment for the ocular surface and providing protection, the scleral lens can be very effective for improving comfort and promoting epithelial healing.[28,29]

Do you have any comments or suggestions about the management of this patient?

Dr Donaldson: When patients are using multiple glaucoma drops, I switch them to a compounded, preservative-free, fixed combination. We work with a few compounding pharmacies that will combine 4 medications in 1 formulation.

I find a scleral lens very helpful in eyes such as these that have not fully responded to other more conservative treatments (such as alleviating medicamentosa, treating with serum tears, and topical anti-inflammatory drops and aggressive preservative-free lubricating drops). We frequently put serum tears in the reservoir if it is available or use the scleral lens over amniotic membrane.

Dr Rapuano: I also often use amniotic membrane in similar cases.

What steroid do you use for controlling inflammation?

Dr Pflugfelder: When possible, I like to have patients get a preservative-free product that is compounded at a local pharmacy. Otherwise, I use prednisolone, loteprednol, or fluorometholone up to 3 times a day.

Dr Donaldson: I worry about the steroid delaying re-epithelialization, but it is often needed because of the severity of the inflammation and vascularization. I usually use loteprednol.

Dr Pflugfelder: A steroid was definitely needed in this case, in which there was corneal vascularization in the context of a graft.

Dr Rapuano: I have patients use the steroid 2 to 4 times daily, depending on the inflammation severity. Although there is a theoretical concern that the steroid will delay healing, I believe any potential risk is outweighed by the benefit for controlling the inflammation. Nevertheless, I have patients return for follow-up within a few days to make sure that their condition is not worsening.

Case 3: Treating Refractory Neurotrophic Keratitis

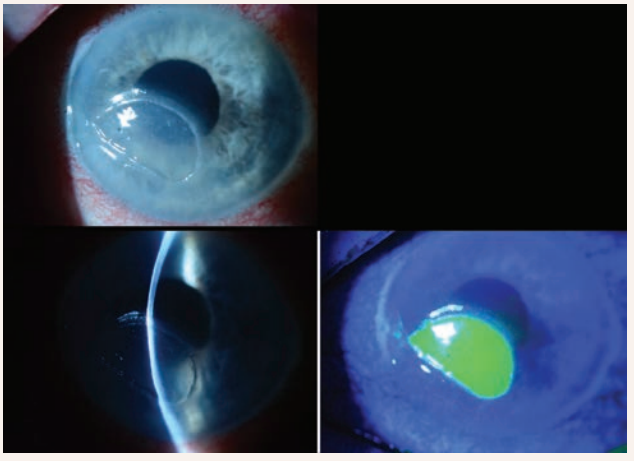
From the Files of Christopher J. Rapuano, MD

A 79-year-old man presented with poor vision OS and a corneal abrasion that was diagnosed 1 week earlier. He developed shingles with OS involvement approximately 20 years ago and had persisting mild postherpetic neuralgia without any sequelae involving his cornea or anterior

segment. The patient was on warfarin for atrial fibrillation. He had cataract surgery OU 10 years ago and several retinal detachment repair surgical procedures OS, with the most recent one done 6 months ago.

He reported developing "conjunctivitis" 3 weeks earlier that was treated with a topical antibiotic. The corneal abrasion was diagnosed 2 weeks later and was treated with a BCL that fell out after 4 days. He was using topical ofloxacin 4 times daily OS.

Slitlamp examination showed a 3.0- × 5.5-mm epithelial defect inferocentrally, with thickened neurotrophic edges, approximately 15% corneal thinning (tissue loss), and haze (Figure 8). He did not have a distinct infiltrate. Corneal sensitivity was decreased OS.



// **FIGURE 8** / 3.0 x 5.0 mm epithelial defect with rolled neurotrophic edges associated with ~15% stromal thinning in the left eye of the patient in Case 3

The patient was diagnosed with Mackie 3 (stromal thinning), ASCRS 5 (ulceration without perforation) NK secondary to herpes zoster ophthalmicus. Treatment was started with a self-retaining double-layer AMT.

Five days later, the epithelial defect was slightly smaller (3 × 4.5 mm). The AMT had dissolved and was replaced. Three days later, the epithelial defect was again only slightly smaller. Treatment was started with valacyclovir 1 g 3 times daily, and the patient was sent for a temporary tarsorrhaphy.

Eight days later, the epithelial defect was only slightly smaller (2.2 × 3.4 mm) and the thinning had progressed to 50% tissue loss. The patient was scheduled for a sutured AMT with repeat temporary tarsorrhaphy, and cenegermin was ordered. He underwent a 3-layered AMT, with a small AMT glued on the epithelial defect and covered with 2 larger AMTs (12 and 16 mm) that were sutured. The tarsorrhaphy and multilayered AMT were intact on postoperative day 1. On postoperative day 9, the tarsorrhaphy was intact, the AMTs were dissolving, and cenegermin 6 times a day was started. He continued antimicrobial treatment with ofloxacin and erythromycin ointment 4 times daily.

// **TABLE 5** / Treatments for Mackie Stage 3 Neurotrophic Keratitis[2]

All stage 1 and stage 2 strategies, plus:

- Amniotic membrane graft (self-retaining or sutured/glued)
- Conjunctival flap

For perforation:

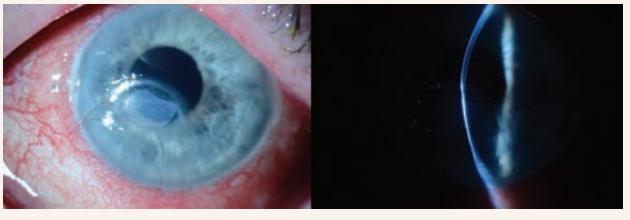
- Corneal grafts (tectonic, lamellar, or full thickness; rarely a posterior lamellar patch graft)
- Cyanoacrylate tissue adhesive with therapeutic contact lens

Dr Rapuano: The therapeutic goal for Mackie stage 3 NK is to promote healing and prevent perforation.[2] Treatment incorporates all strategies used for stage 1 and stage 2 NK and includes additional modalities in the event of perforation **(Table 5)**.[2]

If I am using a single layer of amniotic membrane, I usually suture it over the defect. If, however, I am using multiple amniotic membrane layers, I generally glue a smaller bottom layer over the defect and then suture larger pieces over that.

Dr Pflugfelder: I do the same thing if I am doing a multilayer AMT. I sometimes also place a larger-diameter BCL and do a temporary tarsorrhaphy to maintain the amniotic membrane.

At 2 weeks after starting cenegermin, the tarsorrhaphy was intact, the 2 larger amniotic membranes had dissolved, the epithelium had healed completely over the smallest glued amniotic membrane, and the tarsorrhaphy was opened (Figure 9).



// **FIGURE 9** / Three weeks after placement of the 3-layered AMT and tarsorrhaphy and 2 weeks of treatment with cenegermin, the epithelial defect has completely resolved in the left eye of the patient in Case 3. Note the smallest glued AMT is still present under the healed epithelium.

The patient continued on cenegermin 6 times a day and erythromycin ointment and added preservative-free tears. Two weeks later, the eye was stable and the same treatments were maintained. Approximately 12 weeks later, the eye was stable, erythromycin ointment was discontinued, and valacyclovir dose was decreased to 1 g/d. Preservative-free tears were continued, preservative-free tear gels/ointments were added, and a silicone punctal plug was placed OS in the lower left puncta. Six weeks later (5.5 months postmultilayered AMT and 3 months after completing cenegermin), there was still approximately 50% tissue loss, but the ocular surface was significantly improved (Figure 10). At last follow-up at 2 years, the patient continued to do well while on valacyclovir 1 g/d and frequent lubrication with preservative-free products.

// **FIGURE 10** / Left eye of the patient in Case 3 5.5 months after multilayered AMT/temporary tarsorrhaphy and 3 months after completion of 8-week course of cenegermin; the epithelium remains completely healed

Dr Rapuano: I was really impressed by data from the cenegermin clinical trials showing that it can provide long-term benefit for maintaining corneal integrity.[16,17] Corneal healing can be achieved using tarsorrhaphy or AMT, but the benefit of those modalities is often temporary. In the FDA trial for cenegermin, 80% of corneas that had healed after 8 weeks of treatment were still healed at 48 weeks.[30]

Do you think earlier intervention with AMT and/or cenegermin could have prevented the progression that occurred in this patient?

Dr Donaldson: I think you were fairly aggressive with stepping up your interventions. Once the decision is made to use cenegermin, there is a short waiting period before it is received.

Dr Rapuano: Most patients receive cenegermin within a week, but it can take longer. I tell patients that I cannot say exactly when the cenegermin will arrive, but doing an AMT or tarsorrhaphy certainly provides more immediate treatment.

// TAKE-HOME MESSAGES /

- Neurotrophic keratitis is a degenerative corneal disease hallmarked by reduced corneal sensitivity and impaired corneal healing
- Classification of NK is based on severity and can aid in its early detection and optimal treatment
- Neurotrophic keratitis should be suspected in any eye with a persistent corneal epithelial defect (ie, failure to heal within 1 week)
- Being proactive and intervening early will prevent progression to permanent corneal damage and vision loss
- Treatment of NK is based on the severity and the cause
- Treatment of NK follows a stepladder approach, often employing a combination of medical, nonsurgical, and surgical approaches
- Interventions for NK promote corneal healing by protecting the eye and/or providing regenerative factors
- Management of DED with frequent lubrication and avoiding exposure to potentially toxic topical therapies are integral

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1. Neurotrophic keratitis is a corneal disease characterized by:
   a. Corneal nerve sensitization
   b. Damage to the trigeminal nerve
   c. Elevated levels of nerve growth factor
   d. Elevated levels of substance P

2. The 2 most common causes of NK are:
   a. Cataract surgery and keratoplasty
   b. Contact lens wear and corneal refractive surgery
   c. Diabetes and DED
   d. Herpetic keratitis and postsurgical nerve damage

3. If a patient presents with blurred vision and ocular surface disease, all the following should prompt corneal sensitivity testing to detect NK, EXCEPT:
   a. Absence of symptoms with significant epitheliopathy
   b. PED
   c. Stromal haze
   d. As a routine evaluation for all cataract surgery patients

4. In a phase 2, vehicle-controlled, US clinical trial, 72% of patients treated with cenegermin experienced:
   a. 75% healing of the corneal defect
   b. Complete corneal healing
   c. Complete recovery of corneal sensation
   d. Maintenance of corneal epithelial healing at 52 weeks after completing treatment

5. A patient has been using generic topical timolol maleate for 9 years to treat ocular hypertension and presents with Mackie stage 1 NK OU and meibomian gland dysfunction associated with ocular rosacea. The matrix metalloproteinase-9 assay result is positive. Treatment might include all the following, EXCEPT:
   a. Cenegermin
   b. Oral doxycycline
   c. Switching to a preservative-free IOP-lowering medication
   d. Topical nonsteroidal anti-inflammatory drug

6. A patient with a history of herpetic keratitis is diagnosed with Mackie stage 2 NK when seen on referral. Progression from superficial punctate keratopathy to a frank epithelial defect occurred despite use of a preservative-free ocular lubricant and compliance with oral acyclovir. Which of the following offers the best immediate treatment?
   a. Cenegermin
   b. Corneal neurotization
   c. Cryopreserved self-retaining amniotic membrane
   d. Switching the antiviral treatment to topical acyclovir

7. You receive a call on a Sunday from a patient who is concerned about new onset of eye pain. The patient started treatment with cenegermin 2 weeks earlier for Mackie stage 2 NK. You tell the patient:
   a. The pain is likely a sign of returning corneal sensitization and to increase the frequency of preservative-free ocular lubricants
   b. Stop the cenegermin and go to the emergency department
   c. Increase the frequency of cenegermin dosing to 8 times daily
   d. You will prescribe a topical nonsteroidal anti-inflammatory drug to manage the pain