

NEUROTROPHIC KERATITIS:

Diagnosis, Management, and Future Directions

A comprehensive overview, including clinical diagnosis, staged treatment, and innovative therapies.

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Neurotrophic keratitis (NK) is a rare yet serious degenerative condition characterized by impaired corneal innervation. Typically arising from damage to the trigeminal nerve or its ophthalmic branch, NK can result from various etiologies, including trauma, infection, chemical injury, and surgical insult. The neural impairment disrupts the critical sensory and trophic functions of corneal nerves, precipitating a cascade of events that compromise epithelial integrity and corneal healing.

Clinically, NK progresses through three stages. Mild or stage 1 NK (Figure) reduces tear production, causes punctate epithelial erosions, and impairs corneal reflexes. Moderate or stage 2 NK is characterized by persistent epithelial defects. Severe or stage 3 NK involves stromal ulceration and a risk of perforation if left untreated.¹

A nuanced understanding of NK's pathophysiology and progression is essential for timely diagnosis and targeted therapeutic intervention to preserve patients' vision and corneal health.

DIAGNOSTIC CHALLENGES

Hallmarks

Diagnosing NK can be particularly challenging in its early stages because it often mimics common forms of ocular surface disease (OSD) such as dry eye. The hallmarks of the underlying pathophysiology of NK—reduced corneal neuron activity—include diminished tear production and delayed epithelial healing. Although NK and OSD may share clinical features, several key distinctions can guide the differential diagnosis.

The key sign of NK is a marked reduction in corneal sensation, which can be assessed with tools such as an esthesiometer, cotton swab, or dental floss.² Patients may report minimal discomfort despite significant corneal findings such as punctate epithelial erosions and persistent defects. NK often presents as severe unilateral punctate keratopathy that is out of proportion to the patient's symptoms.

Impaired innervation reduces the blink reflex and promotes tear film instability, leading to characteristic central corneal staining in the exposed interpalpebral zone.



Comprehensive Assessment

A thorough review of the patient's medical and surgical history can help identify risk factors for NK. These include a history of herpes simplex virus or varicella zoster virus infection, ocular surgery (eg, LASIK, PRK), and systemic conditions such as diabetes mellitus and multiple sclerosis as well as potential exposure to neurotoxic agents such as benzalkonium chloride in topical medications.^{3,4}

MANAGEMENT CONSIDERATIONS IN THE CONTEXT OF SURGERY

The timely diagnosis and management of NK are critical, particularly for patients undergoing ocular surgery. Impaired corneal healing can complicate surgical outcomes, requiring tailored perioperative strategies. Key considerations include aggressive lubrication, the use of amniotic membranes to promote healing, and avoiding topical nonsteroidal antiinflammatory drugs.⁵ Preoperative optimization of the ocular surface is equally important because untreated NK and other OSDs can affect the accuracy of keratometry readings and visual outcomes.⁶ Corneal staining, reduced tear breakup time, and subjective dryness must be addressed to minimize surgical risks and enhance patient satisfaction.

MANAGEMENT

Immediate and proactive management is required to prevent NK progression and mitigate vision-threatening complications. Treatment is tailored to the disease stage and emphasizes corneal protection, epithelial healing, and nerve regeneration.

Stage No. 1: Ocular Surface Stabilization

In early-stage NK, treatment focuses on aggressive lubrication with preservative-free artificial tears administered every 1 to 2 hours during waking hours to minimize exposure to benzalkonium chloride and other preservatives. Bandage contact lenses can provide a physical barrier to protect the epithelium from irritation caused by the eyelids and environmental debris. Autologous serum tears

offer a biologically active alternative, supplying antiinflammatory cytokines, nerve growth factors, and essential molecules such as interleukin-1 receptor antagonist, epidermal growth factor, and transforming growth factor-beta to support corneal epithelial regeneration and nerve repair.^{7,8}

Stage No. 2: Ulceration Prevention

When epithelial defects are present but no ulceration has occurred, the primary goals of treatment are to prevent infection and promote epithelial healing. Therapies initiated in stage 1 (lubrication, bandage contact lenses, autologous serum tears) should be continued. Additional measures include the administration of topical antibiotics to guard against infection and the cautious use of topical corticosteroids to control inflammation without exacerbating stromal melting. Cryopreserved amniotic membrane tissues, such as Prokera (BioTissue), have demonstrated efficacy in promoting corneal healing by delivering growth factors and antiinflammatory cytokines while providing a protective barrier for epithelial regeneration.⁹

Stage No. 3: Advanced Interventions for Severe Cases

For moderate to severe NK, cenegermin (Oxervate, Dompé), a recombinant human nerve growth factor, is a cornerstone therapy.^{10,11} Applied six times daily for 8 weeks, cenegermin has been shown to promote corneal nerve regeneration, enhance corneal sensitivity, and sustain epithelial healing, even in eyes with advanced disease.

If conventional treatments prove insufficient, corneal neurotization surgery may be considered.¹² A donor nerve, such as the supraorbital or sural nerve, is redirected to restore corneal sensation.

EMERGING THERAPY

Clinical trials of KPI-012 (Kala Pharmaceuticals) are underway. This mesenchymal stem cell-derived secretome therapy has been designed to enhance corneal healing by delivering bioactive molecules that promote tissue regeneration. If approved, the

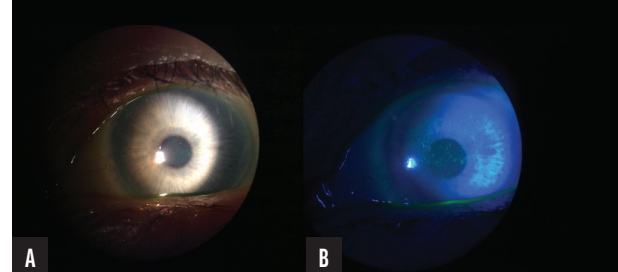


Figure. Stage 1 NK. The eye of a patient with a history of NK (A). Under cobalt blue illumination with fluorescein staining, the image shows the characteristic findings of stage 1 NK, including punctate epithelial erosions without epithelial defects or stromal involvement (B).

drug could revolutionize the treatment of persistent epithelial defects characteristic of stage 2 NK.

CONCLUSION

With a comprehensive, staged approach and the integration of emerging therapies, ophthalmologists are increasingly well equipped to manage NK effectively. Early diagnosis and timely intervention are critical to halting disease progression and preserving patients' vision. The multidisciplinary collaboration and innovation driving NK research and clinical practice promise an improved prognosis for patients. ■

The author used ChatGPT version 4 (OpenAI) to assist in the creation of this article.

1. Feroze KB, Patel BC. Neurotrophic keratitis. In: *StatPearls*. StatPearls Publishing; August 8, 2023.
2. Villalba M, Sabates V, Orgul S, Perez VL, Swaminathan SS, Sabater AL. Detection of subclinical neurotrophic keratopathy by noncontact esthesiometry. *Ophthalmol Ther*. 2024;13(3):2393-2404.
3. Datta S, Baudouin C, Brignole-Baudouin F, Denoyer A, Cortopassi GA. The eye drop preservative benzalkonium chloride potentially induces mitochondrial dysfunction and preferentially affects Thon mutant cells. *Invest Ophthalmol Vis Sci*. 2017;58(4):2406-2412.
4. Sarkar J, Chaudhary S, Namavari A, et al. Corneal neurotoxicity due to topical benzalkonium chloride. *Invest Ophthalmol Vis Sci*. 2012;53(4):1792-1802.
5. Raj N, Panigrahi A, Alam M, Gupta N, Bromfenac-induced neurotrophic keratitis in a corneal graft. *BMJ Case Rep*. 2022;15(7):e249400.
6. Yang F, Yang L, Ning X, Liu J, Wang J. Effect of dry eye on the reliability of keratometry for cataract surgery planning. *J Fr Ophthalmol*. 2024;47(2):103999.
7. Matsumoto Y, Dogru M, Goto E, et al. Autologous serum application in the treatment of neurotrophic keratopathy. *Ophthalmology*. 2004;111(6):1115-1120.
8. Aggarwal S, Colon K, Kheirikhah A, Hamrah P. Efficacy of autologous serum tears for treatment of neurotrophic corneal pain. *Ocul Surf*. 2019;17(3):532-539.
9. Mead OG, Tighe S, Tseng SCG. Amniotic membrane transplantation for managing dry eye and neurotrophic keratitis. *Taiwan J Ophthalmol*. 2020;10(1):13-21.
10. 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.
11. 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.
12. Swanson MA, Swanson RD, Koitha VS, et al. Corneal neurotization: a meta-analysis of outcomes and patient selection factors. *Ann Plast Surg*. 2022;88(6):687-694.

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- Financial disclosure: None