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Infectious Keratitis in 2021

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The cornea transmits light and provides approximately two-thirds of the eye's focusing power. Corneal infection, also called infectious keratitis, can cause vision loss through corneal scarring or perforation. Keratitis, mostly due to infection, is estimated to account for approximately 1 million health care visits in the US annually.[1] Symptoms include photophobia and unilateral eye pain, redness, and decreased vision. Sudden onset of eye pain or reduced vision requires prompt (<24 hours) referral to an ophthalmologist. Infectious keratitis can be categorized into microbial (bacterial, fungal, or parasitic) or viral keratitis. Microbial keratitis is often called infectious corneal ulcer.

Microbial Keratitis

The major risk factor for microbial keratitis in the US is use of contact lenses, worn by approximately 45 million residents (**Figure**).[1] The estimated incidence of microbial keratitis cases per 100 000 person-years in the US in 2010 was 130 among contact lens wearers vs 14 among nonwearers.[2] Many corneal infections can be prevented through proper contact lens care. Poor lens care is common and includes sleeping in the lenses, storing them in tap water, and reusing the same lens case for prolonged periods.[1] Other risk factors for microbial keratitis include eye trauma, such as corneal abrasions, and chronic ocular surface diseases, such as severe dry eye.

Flashlight examination may reveal conjunctival injection and a white opacity in the cornea. Slit lamp examination reveals the extent of the keratitis. Intraocular inflammation, if present, appears as white blood cells dispersed in the aqueous or layered in the base of the anterior chamber (hypopyon). Intraocular inflammation in keratitis is usually sterile but rarely may represent endophthalmitis (intraocular infection), a particular concern with full-thickness corneal infections.

Bacteria cause approximately 90% of microbial keratitis in regions with high rates of contact lens wear (such as the US), and the major pathogens are *Pseudomonas*, *Staphylococcus aureus,* and streptococci. *Pseudomonas* may cause more than 40% of contact lens–related corneal ulcers,[3] and *Pseudomonas* keratitis is often severe. Other causes of keratitis include fungi and *Acanthamoeba*. Molds, most often *Fusarium* or *Aspergillus*, cause as many as half of keratitis cases in tropical regions of the world such as southern and southeast Asia.[4] In the US, eye trauma and contact lens wear are major risk factors for keratitis due to molds. Corneal ulcers caused by molds often have indistinct borders and satellite lesions. *Candida* primarily causes keratitis in patients with chronic ocular surface disease. *Acanthamoeba* is a genus of free-living amoebae that may be present in tap water and can contaminate contact lens cases. Approximately 85% of *Acanthamoeba* keratitis infections in the US occur among contact lens wearers.[1] A typical feature is marked eye pain out of proportion to the extent of corneal inflammation. Some patients are misdiagnosed as having herpes simplex virus (HSV) keratitis. Perineural corneal infiltrates may be seen in early cases of *Acanthamoeba* keratitis, a ring corneal infiltrate in advanced cases.

Patients who wear contact lenses should remove them if microbial keratitis is suspected. Treatment involves frequent antibiotic eye drops (eg, hourly for 2 days tapering to every 4 hours by day 7). Ointments generally provide insufficient antibiotic concentrations. Initial treatment is usually empirical, with topical fluoroquinolones or compounded antibiotics, typically cefazolin or vancomycin plus tobramycin, for suspected bacterial keratitis. Antibiotic choice may be modified based on culture results; pathogen-specific treatment recommendations have been previously published.[5] Fungal keratitis should be treated with topical antifungal agents such as natamycin; oral antifungal agents, such as voriconazole, are added in some cases. *Acanthamoeba* keratitis treatment options are limited and include topical chlorhexidine and polyhexamethylene biguanide; therapeutic corneal transplantation is often necessary. Treatment failures for microbial keratitis may occur if the infection is due to antibiotic-resistant pathogens or if patients are unable to administer eye drops. Repeat cultures and hospital admission for eye drop administration may be indicated.

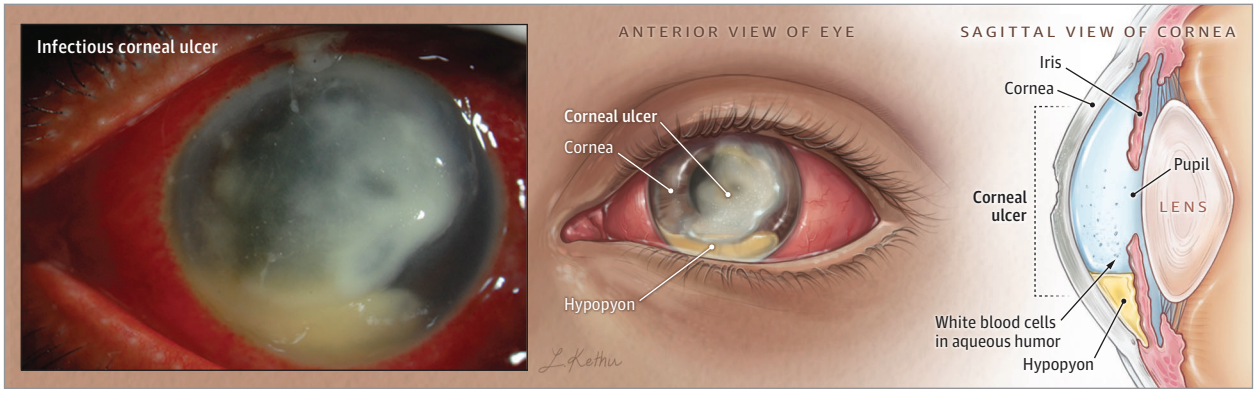
Viral Keratitis

The 2 major causes of viral keratitis are HSV and varicella-zoster virus (VZV). Most HSV keratitis results from reactivation of latent HSV type 1 from the trigeminal ganglion. According to a report from 2012, HSV caused an estimated 1.5 million keratitis cases and 40 000 cases of impaired vision annually worldwide.[6] VZV typically causes keratitis in the setting of herpes zoster ophthalmicus (herpes zoster in the distribution of the trigeminal nerve's ophthalmic division), and herpes zoster ophthalmicus comprises 8% of the estimated 1 million cases of herpes zoster in the US each year.[7,8] Keratitis occurs in 13% to 76% of herpes zoster ophthalmicus cases.[8,9]

Slit lamp examination of an eye with HSV keratitis reveals either a dendritic or geographic pattern of epithelial ulceration, or it reveals an infiltrate in the corneal stroma. HSV epithelial keratitis is treated with a topical (eg, ganciclovir gel) or an oral antiviral agent (eg, acyclovir). The other forms of HSV keratitis are treated with a combination of corticosteroid eye drops and oral antiviral agents. HSV keratitis recurrence is common, but chronic acyclovir prophylaxis reduces the frequency.

VZV can cause manifestations in the cornea similar to those caused by HSV. Acute VZV keratitis typically occurs within 1 month of herpes zoster ophthalmicus onset.[8] Herpes zoster ophthalmicus usually manifests as a unilateral vesicular rash involving the upper face; vesicles on the nasal tip or sides are present in approximately one-fifth of patients and may correlate with eye involvement. Patients with herpes zoster ophthalmicus should be referred to an ophthalmologist; referral should be urgent if there are ocular symptoms or signs such as pain, redness, or blurred

Figure. Views of the Eye With Infectious Corneal Ulcer



Bacterial keratitis with ulceration (due to *Pseudomonas*) in a contact lens wearer. Some cases, as shown in this Figure, may have intraocular inflammation consisting of white blood cells in the aqueous with or without a hypopyon. Intraocular inflammation in keratitis is usually sterile.

vision. Early findings in herpes zoster ophthalmicus–related keratitis include punctate epithelial keratitis and pseudodendrites; stromal infiltrates follow in approximately half of patients and may lead to corneal scars.[8] Moderate to complete corneal anesthesia complicates herpes zoster ophthalmicus–related keratitis in approximately 60% of cases and can lead to complications such as neurotrophic corneal ulceration, superinfection, scarring, or perforation. Acute herpes zoster ophthalmicus is treated with an oral antiviral agent (acyclovir, valacyclovir, or famciclovir). Vaccination with recombinant zoster vaccine is highly effective in preventing zoster (97% efficacy for ages 50-69 years, 91% for age ≥70).[10]

Conclusion

Contact lens wear is a major risk factor for microbial keratitis in the US, and good lens care may reduce the incidence. HSV and VZV are the major etiologies of viral keratitis; recombinant zoster vaccine may reduce the incidence of VZV keratitis.

ARTICLE INFORMATION

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REFERENCES

1. Centers for Disease Control and Prevention. Healthy contact lens wear and care. Accessed December 17, 2020. https://www.cdc.gov/contactlenses/fast-facts.html

2. Jeng BH, Gritz DC, Kumar AB, et al. Epidemiology of ulcerative keratitis in Northern California. *Arch Ophthalmol*. 2010;128(8):1022-1028. doi:10.1001/archophthalmol.2010.144

3. Bennett L, Y Hsu H, Tai S, et al. Contact lens versus non-contact lens-related corneal ulcers at an academic center. *Eye Contact Lens*. 2019;45(5):301-305. doi:10.1097/ICL.0000000000000568

4. Ung L, Bispo PJM, Shanbhag SS, Gilmore MS, Chodosh J. The persistent dilemma of microbial keratitis: global burden, diagnosis, and antimicrobial resistance. *Surv Ophthalmol*. 2019;64(3):255-271. doi:10.1016/j.survophthal.2018.12.003

5. Lin A, Rhee MK, Akpek EK, et al; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Bacterial keratitis preferred practice pattern. *Ophthalmology*. 2019;126(1):P1-P55. doi:10.1016/j.ophtha.2018.10.018

6. Farooq AV, Shukla D. Herpes simplex epithelial and stromal keratitis: an epidemiologic update. *Surv Ophthalmol*. 2012;57(5):448-462. doi:10.1016/j.survophthal.2012.01.005

7. Kong CL, Thompson RR, Porco TC, Kim E, Acharya NR. Incidence rate of herpes zoster ophthalmicus: a retrospective cohort study from 1994 through 2018. *Ophthalmology*. 2020;127(3):324-330. doi:10.1016/j.ophtha.2019.10.001

8. Li JY. Herpes zoster ophthalmicus: acute keratitis. *Curr Opin Ophthalmol*. 2018;29(4):328-333. doi:10.1097/ICU.0000000000000491

9. Yawn BP, Wollan PC, St Sauver JL, Butterfield LC. Herpes zoster eye complications: rates and trends. *Mayo Clin Proc*. 2013;88(6):562-570. doi:10.1016/j.mayocp.2013.03.014

10. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67(3):103-108. doi:10.15585/mmwr.mm6703a5