Viral Keratitis

Abstract

Keratitis is the inflammation of the cornea. The inflammation is secondary to the infection. Viruses have ambiguous characteristics’, It behaves as living when entering a living body due to the presence of DNA double strands or single-stranded RNA. The major cause of superficial keratitis are those caused by viruses. The most common being Herpes zoster and adenovirus. The sign ranges from superficial punctate epithelial defect to circum corneal injection, and endothelial infiltrates with hypopyon. The symptoms can be minor as watering to severe pain.The treatment of the viral keratitis is based on the clinical presentation and symptoms. Anti viral tropical drops can be helpful with artificial tear, but it can be the combination of drops with oral medication and sometimes even surgical intervention is required. Its important to know the pathophysiology of the causative agent to control the multiplication thus minimising the corneal defect.

Keywords: viral keratitis, pathophysiology, circum corneal injections, symptom, superficial puntate keratitis.

Introduction

Viral Keratitis is the commonest cause of keratitis in the developing world. The reason was primarily attributed to the poorer environmental and personal hygiene, lower level of education, agricultural industry, increased risk to work-related corneal trauma and poorer access to sanitation and healthcare facility.[1] The virus can infect individual layers of the cornea or may involve all layers in a more severe form. Viral keratitis is broadly grouped under Herpes Simplex keratitis and Herpes Zoster Ophthalmicus. Herpes simplex virus (HSV) is very common and remains the leading infectious cause of corneal ulcers and blindness worldwide.[1]

Globally, the incidence of HSV keratitis is 1.5 million yearly, including 40,000 new cases that result in severe visual impairment. [2] Herpes simplex virus keratitis (HSK) is a leading cause of monocular infectious blindness in developed countries due to stromal opacification.[2] HSV exist in type 1 (HSV-1) and type-2 (HSV-2). Worldwide, an estimated 4.85 billion people of all ages have prevalent HSV-1 infection.[3]

Infection with HSV is life-long and is characterized by periodic recurrences of the disease in a proportion of those infected.HSV-1 is predominantly transmitted by the oral route, establishes latency in the trigeminal ganglion and is associated with orolabial, ocular and neurological conditions.HSV-2 is almost exclusively a sexually transmitted infection which establishes latency in the sacral ganglia and is associated with genital ulcer disease.

Primary keratitis typically occurs in childhood and is spread by direct contact.Recurrent HSV keratitis can also present as epithelial keratitis. Epithelial keratitis is involved in two-thirds of the cases. The earliest sign of epithelial disease includes raised clear vesicles that later coalesce to form the classic dendritic lesion. The hallmark of HSV epithelial is the presence of a dendritic ulcer. The dendritic ulcer may evolve into geographic ulceration, especially in patients with compromised immunity, atopy, or on topical steroids. Ocular pain is often a hallmark of HSV epithelial keratitis, as it tends to be the most painful form of HSV keratitis.Other symptoms include blurred vision, photophobia, pain, redness, and/or tearing.

Herpes Zoster Ophthalmicus (HZO) is a viral disease characterized by a unilateral painful skin rash in one or more dermatome distributions of the fifth cranial nerve (trigeminal nerve), shared by the eye and ocular adnexa. The incidence and severity of HZ increase with advancing age.[4] Immune system status plays a role, patients that are treated with immunosuppressive drugs have a significantly increased risk for herpes zoster. [[5]](https://eyewiki.aao.org/Herpes_Zoster_Ophthalmicus#cite_note-cohen-4) Corneal involvement includes both epithelial keratitis and stromal keratitis. Pseudodendrites appear as branching lesions similar to the true dendritic lesions seen in herpes simplex virus (HSV) keratitis. Unlike the dendrites of HSV, HZO pseudodendrites are non-erosive mucous plaques that exhibit minimal staining with an absence of terminal bulbs. Stromal keratitis may be classified as anterior or deep and usually develops after epithelial keratitis. Anterior stromal keratitis results from an immune-mediated response to the virus and is characterized by nummular (coin-shaped) granules in the superficial stroma. Deep stromal keratitis usually occurs late in the disease course and presents with marked corneal oedema often associated with anterior uveitis.

**Pathophysiology of Viral Keratitis**

The pathophysiology of viral keratitis involves a complex interplay between the virus and the host's immune system. In this article, we will discuss the pathophysiology of viral keratitis in detail.

The cornea is the clear, dome-shaped outermost layer of the eye, which plays a crucial role in vision. Viral keratitis typically affects the epithelial layer of the cornea, which is the outermost layer that covers the cornea. It is caused by several types of viruses. The most common causative agents of viral keratitis are the herpes simplex virus (HSV) and varicella-zoster virus (VZV), although other viruses such as adenovirus, cytomegalovirus, and Epstein-Barr virus can also cause the disease. The pathophysiology of viral keratitis is complex and involves a combination of viral replication, tissue destruction, and immune responses.The pathogenesis of viral keratitis begins with the attachment and entry of the virus into the host corneal epithelium. This process is facilitated by viral glycoproteins that interact with specific host cell surface receptors. Once inside the host cell, the virus uses its own genetic machinery to replicate and produce more virus particles, which in turn infect adjacent cells.

As the virus replicates within the host corneal epithelium, it induces a cascade of cellular and molecular events that contribute to the pathophysiology of viral keratitis. The viral replication process damages host cells, leading to the release of cytokines, chemokines, and other pro-inflammatory molecules. These molecules initiate a local inflammatory response, which attracts immune cells to the site of infection.Neutrophils and macrophages are among the first immune cells to arrive at the site of viral infection. These cells play an essential role in the early stages of the immune response, as they can recognize and eliminate virus-infected cells through phagocytosis and the release of cytotoxic substances. However, viruses have evolved mechanisms to evade the host immune response, such as by encoding viral proteins that interfere with the function of host immune cells.

The immune response to viral keratitis can lead to a range of clinical manifestations, depending on the severity and duration of the infection. In some cases, the immune response can be overwhelming, leading to extensive tissue damage and the development of severe corneal ulceration or perforation. The chronic immune-mediated response can also lead to corneal scarring and neovascularization, which can impair vision.

In conclusion, the pathophysiology of viral keratitis is complex and involves a combination of viral replication, tissue destruction, and immune responses. Understanding the mechanisms of viral pathogenesis and host immune response is essential for the development of effective treatments and prevention strategies. The management of viral keratitis requires a multidisciplinary approach involving ophthalmologists, infectious disease specialists, and immunologists.

**Treatments:**

**Topical Treatment**

Viral Keratitis is one of the prevalent infectious keratitis characterized by total or partial loss of vision. The most common etiological agents for causing viral keratitis are viruses of which HSV, CMV, VZV, and EBV are the most common. Antiviral medications and adjuvant topical steroids are the most common topical treatments involved. Antiviral medications can be classified into two basic categories: antiviral nucleoside analogs and glucocorticoids. Topical treatment for viral keratitis includes topical trifludine which is most commonly prescribed for HSV keratitis in the United States. Apart from this newer topical antiviral medication are also developed due to the lower bioavailability and so caused ocular toxicity and hence to reduce this ocular toxicity acyclovir is been used as the first line treatment for HSV keratitis in Europeans which is found to be just as effective as trifluridine. Ganciclovir has proved to show antiviral coverage to a greater spectrum including HSV and VZV keratitis apart from this causing less ocular toxicity. It is also likely to produce less drug resistance. Multiple analogues includes, cidofovir, brincidofovir, valacyclovir, and trifluridine. Each of them possesses their own unique set of advantages. In a study it was shown prophylactic acyclovir reducing the recurrence of keratitis by 32%. Randomized control trial investigation is been conducted North western university for the treatment purpose of VZV keratitis.

Glucocorticoids are also prescribed for the treatment of keratitis wherein topical corticosteroids are used as an adjuvant therapy to that of the topical antiviral treatment. The Herpetic Eye Disease Study (HEDS1 ) study was conducted to evaluate the efficacy of oral acyclovir in treating stromal keratitis caused by the HSV virus. In a randomized control trial with 106 patients either subjected to topical prednisolone phosphate or placebo which was tapered over a period of 10 week it was found that the treatment failure was found to be drastically shorter in placebo group.Time taken for resolution of an infection is seen shorter in group receiving topical corticosteroid with a median of 26 days and 72 days for those taking placebo.

**Oral Treatment**

The HEDS 1 trial study also investigated oral acyclovir as an adjuvant treatment for HSV stromal keratitis which is studies is found that long term oral acyclovir therapy reduces the rate of recurrent HSV epithelial keratitis and stromal keratitis with a long term benefit for patients with HSV stromal keratitis. In an Randomized control study done one hundred and four patients receiving both topical trifluridine and corticosteroid were randomized to receive either placebo or 200mg of oral acyclovir given 5 times daily for 10 weeks wherein the result was not found to be statistically significant (p=0.46).A delayed treatment failure was seen ( 62 days in placebo and 84 days in acyclovir group).Oral acyclovir is found to be efficacious against VZV keratitis. In a study was shown the cumulative probability of recurrence of HSV in 1 year of treatment is 19% as compared to the placebo group that is 32%.

Valacyclovir is seen to new treatment modality which is well tolerated and has a better ocular penetration. The treatment dose basically includes 1gm for three times daily as compared to the acyclovir that is 400mg for fives times daily. Whereas for VZV it is 800mg five times daily.Oral Valganciclovir is preferred choice of treatment for CMV stromal keratitis but has long term significant side effects like aplastic anemia that needs to be closely monitored. It is the pro-drug of ganciclovir, thus has better intestinal absorption quality and higher biocompatibility.Oral antivirals are generally used in practice to avoid the ocular toxicity.topical medications are used as an adjuvant when oral medications do not perform well for patients with systemic illness.

References.

# [Malik Moledina](https://www.nature.com/articles/s41433-023-02404-3#auth-Malik-Moledina), ,[Harry W. Roberts](https://www.nature.com/articles/s41433-023-02404-3" \l "auth-Harry_W_-Roberts), et.el, Analysis of microbial keratitis incidence, isolates and in-vitro antimicrobial susceptibility in the East of England: a 6-year study, eye 2023, doi.org/10.1038/s41433-023-02404-3

1. Ahmad B, Patel BC. Herpes Simplex Keratitis. [Updated 2022 Aug 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022
2. Farooq, A. V., & Shukla, D. (2012). Herpes simplex epithelial and stromal keratitis: an epidemiologic update. *Survey of ophthalmology*, *57*(5), 448–462.
3. McCormick, I., James, C., Welton, N. J., Mayaud, P., Turner, K. M. E., Gottlieb, S. L., Foster, A., & Looker, K. J. (2022). INCIDENCE OF HERPES SIMPLEX VIRUS KERATITIS AND OTHER OCULAR DISEASE: GLOBAL REVIEW AND ESTIMATES. *Ophthalmic epidemiology*, *29*(4), 353–362.
4. Cohen PR, Grossman ME. Clinical features of human immunodeficiency virus-associated disseminated herpes zoster virus infection--a review of the literature. Clin Exp Dermatol. 1989 Jul;14(4):273-6. doi: 10.1111/j.1365-2230.1989.tb01978.x. PMID: 2686873.
5. Sampathkumar, P., Drage, L. A., & Martin, D. P. (2009). Herpes zoster (shingles) and postherpetic neuralgia. *Mayo Clinic proceedings*, *84*(3), 274–280. https://doi.org/10.1016/S0025-6196(11)61146-4

7. Morfin F, Thouvenot D. Herpes simplex virus resistance to antiviral drugs. *Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology.*2003 Jan;26(1):29–37. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/12589832)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Journal+of+clinical+virology:+the+official+publication+of+the+Pan+American+Society+for+Clinical+Virology&title=Herpes+simplex+virus+resistance+to+antiviral+drugs&author=F+Morfin&author=D+Thouvenot&volume=26&issue=1&publication_year=2003&pages=29-37&pmid=12589832&)]

8. Tsatsos M, MacGregor C, Athanasiadis I, Moschos MM, Hossain P, Anderson D. Herpes simplex virus keratitis: an update of the pathogenesis and current treatment with oral and topical antiviral agents. *Clinical & experimental ophthalmology.*2016 Dec;44(9):824–837. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/27273328)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Clinical+&+experimental+ophthalmology&title=Herpes+simplex+virus+keratitis:+an+update+of+the+pathogenesis+and+current+treatment+with+oral+and+topical+antiviral+agents&author=M+Tsatsos&author=C+MacGregor&author=I+Athanasiadis&author=MM+Moschos&author=P+Hossain&volume=44&issue=9&publication_year=2016&pages=824-837&pmid=27273328&)]

9. Chou TY, Hong BY. Ganciclovir ophthalmic gel 0.15% for the treatment of acute herpetic keratitis: background, effectiveness, tolerability, safety, and future applications. *Therapeutics and clinical risk management.*2014;10:665–681. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4149409/)] [[PubMed](https://pubmed.ncbi.nlm.nih.gov/25187721)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Therapeutics+and+clinical+risk+management&title=Ganciclovir+ophthalmic+gel+0.15%25+for+the+treatment+of+acute+herpetic+keratitis:+background,+effectiveness,+tolerability,+safety,+and+future+applications&author=TY+Chou&author=BY+Hong&volume=10&publication_year=2014&pages=665-681&pmid=25187721&)]

10. Colin J, Hoh HB, Easty DL, et al. Ganciclovir ophthalmic gel (Virgan; 0.15%) in the treatment of herpes simplex keratitis. *Cornea.*1997 Jul;16(4):393–399. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/9220235)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Cornea&title=Ganciclovir+ophthalmic+gel+(Virgan;+0.15%25)+in+the+treatment+of+herpes+simplex+keratitis&author=J+Colin&author=HB+Hoh&author=DL+Easty&volume=16&issue=4&publication_year=1997&pages=393-399&pmid=9220235&)]

11. Wilhelmus KR, Gee L, Hauck WW, et al. Herpetic Eye Disease Study. A controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology.*1994 Dec;101(12):1883–1895. discussion 1895-1886. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/7997324)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Ophthalmology&title=Herpetic+Eye+Disease+Study.+A+controlled+trial+of+topical+corticosteroids+for+herpes+simplex+stromal+keratitis&author=KR+Wilhelmus&author=L+Gee&author=WW+Hauck&volume=101&issue=12&publication_year=1994&pages=1883-1895&pmid=7997324&)]

12. Barron BA, Gee L, Hauck WW, et al. Herpetic Eye Disease Study. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology.*1994 Dec;101(12):1871–1882. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/7997323)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Ophthalmology&title=Herpetic+Eye+Disease+Study.+A+controlled+trial+of+oral+acyclovir+for+herpes+simplex+stromal+keratitis&author=BA+Barron&author=L+Gee&author=WW+Hauck&volume=101&issue=12&publication_year=1994&pages=1871-1882&pmid=7997323&)]

13. Goldblum D, Bachmann C, Tappeiner C, Garweg J, Frueh BE. Comparison of oral antiviral therapy with valacyclovir or acyclovir after penetrating keratoplasty for herpetic keratitis. *The British journal of ophthalmology.*2008 Sep;92(9):1201–1205. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/18650215)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=The+British+journal+of+ophthalmology&title=Comparison+of+oral+antiviral+therapy+with+valacyclovir+or+acyclovir+after+penetrating+keratoplasty+for+herpetic+keratitis&author=D+Goldblum&author=C+Bachmann&author=C+Tappeiner&author=J+Garweg&author=BE+Frueh&volume=92&issue=9&publication_year=2008&pages=1201-1205&pmid=18650215&)]

14. Dias C, Nashed Y, Atluri H, Mitra A. Ocular penetration of acyclovir and its peptide prodrugs valacyclovir and val-valacyclovir following systemic administration in rabbits: An evaluation using ocular microdialysis and LC-MS. *Current eye research.*2002 Oct;25(4):243–252. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/12658558)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Current+eye+research&title=Ocular+penetration+of+acyclovir+and+its+peptide+prodrugs+valacyclovir+and+val-valacyclovir+following+systemic+administration+in+rabbits:+An+evaluation+using+ocular+microdialysis+and+LC-MS&author=C+Dias&author=Y+Nashed&author=H+Atluri&author=A+Mitra&volume=25&issue=4&publication_year=2002&pages=243-252&pmid=12658558&)]

15. Razonable RR. Antiviral drugs for viruses other than human immunodeficiency virus. *Mayo Clinic proceedings.*2011 Oct;86(10):1009–1026. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3184032/)] [[PubMed](https://pubmed.ncbi.nlm.nih.gov/21964179)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Mayo+Clinic+proceedings&title=Antiviral+drugs+for+viruses+other+than+human+immunodeficiency+virus&author=RR+Razonable&volume=86&issue=10&publication_year=2011&pages=1009-1026&pmid=21964179&)]

16. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Herpetic Eye Disease Study Group. *The New England journal of medicine.*1998 Jul 30;339(5):300–306. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/9696640)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=The+New+England+journal+of+medicine&title=Acyclovir+for+the+prevention+of+recurrent+herpes+simplex+virus+eye+disease&volume=339&issue=5&publication_year=1998&pages=300-306&pmid=9696640&)]

17. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. *Lancet.*2002 Aug 31;360(9334):678–682. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/12241874)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Lancet&title=Contacts+with+varicella+or+with+children+and+protection+against+herpes+zoster+in+adults:+a+case-control+study&author=SL+Thomas&author=JG+Wheeler&author=AJ+Hall&volume=360&issue=9334&publication_year=2002&pages=678-682&pmid=12241874&)]