

# Herpes Simplex Epithelial Keratitis and Proposed Treatments

Andrea De Souza, OD



## Author's Bio

Dr. Andrea De Souza received her Doctor of Optometry Degree in 2012 from the New England College of Optometry in Boston, MA. She continued her optometric training and graduated from the Primary Care and Contact Lens residency at the UC Berkeley School of Optometry in 2013. Today, Dr. De Souza works as a clinical instructor at the UC Berkeley School of Optometry teaching students in the field of ocular disease, contact lens and primary care.

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## I. Introduction

**H**erpes simplex virus (HSV) stromal keratitis is the leading infectious cause of corneal blindness in developed nations. In the United States alone, approximately 46,000 cases of HSV ocular infection are diagnosed each year.<sup>1</sup>

HSV is divided into two categories: type 1 and type 2. HSV-1, which most commonly infects the mouth and eyes, is transmitted through direct contact of skin sores or oral secretions, often via kissing. HSV-2 typically affects the genitals and is most commonly transmitted in adults through sexual contact or via maternal transmission to newborns during childbirth.<sup>2</sup> HSV-2 is thought to infect over 500 million people worldwide and approximately 23 million new cases are reported each year; the incidence of HSV-1 infections, however, are even greater.<sup>2</sup>

More than 80% of individuals carry herpes simplex virus antibodies, however 94% of primary infections are subclinical.<sup>3</sup> Most primary initial infections occur between the ages of six months and five years. Once infected, the virus travels along nerves from the skin and mouth to the dorsal root of the trigeminal ganglion, via axoplasmic transport, and lays dormant. Primary ocular HSV typically manifests as unilateral lid vesicles and erosive blepharitis, epithelial keratitis, or most commonly, follicular or pseudomembraneous conjunctivitis.<sup>4</sup> The virus may later reactivate following physical or emotional stress, fatigue, local trauma, ultraviolet exposure, extreme temperatures, certain medications, fever, menstruation, or immunocompromised states.<sup>5</sup>

Upon reactivation, the virus replicates and travels along the (ophthalmic branch of the) trigeminal nerve to the cornea (via the short and long ciliary nerves). Recurrent HSV keratitis can present in one of four ways: epithelial keratitis, neurotrophic keratitis, stromal keratitis or endotheliitis. Although most cases do not recur, Saini and Argawala found that there is a 36% chance for a second recurrence within the first year. Additionally,

chances of recurrence is greater if the first two episodes are closer together.<sup>6</sup> Also, if the first episode of HSV keratitis is severe, the recurring episodes are likely to be severe as well.<sup>6</sup>

## **II. Case**

A 22 year-old female presented with a primary complaint of pain in the right eye after sleeping in her one-month soft contact lenses two nights prior to her visit. Upon waking she also experienced mild yellow mucous discharge, photophobia, redness, dryness and irritation of both eyes, right worse than left. Her ocular history was unremarkable and medical history was remarkable for asthma and occasional migraine headaches. She denied use of or allergies to medications.

Upon examination her entering best-corrected visual acuity was 20/20 in the right and left eye. Pupils and extra-ocular motilities were normal. Anterior segment evaluation of the right eye revealed grade 2+ diffuse hyperemia of the bulbar conjunctiva, grade 1+ hyperemia of the superior and inferior palpebral conjunctiva and grade 3+ pancorneal elevated stellate epithelial lesions, 75% of which positively stained with fluorescein and Rose Bengal (Figure 3 and 4). The left eye revealed grade 1 diffuse bulbar conjunctival hyperemia, grade 1+ hyperemia of the superior and inferior palpebral conjunctiva and grade 1 elevated stellate, epithelial lesions, the majority of which stained with fluorescein but not Rose Bengal (Figure 6). This patient was diagnosed with bilateral HSV stellate epithelial keratitis. She was prescribed 800mg of acyclovir five times daily for ten days, advised to discontinue contact lens wear, and return for follow-up in 24 hours.

At her 24 hour follow-up she reported increased pain and burning sensation in both eyes and the photophobia had remained unchanged. She presented with 2+ upper lid edema in the right eye and no improvement in conjunctival hyperemia or corneal lesions in both eyes. The stellate lesions of the inferior cornea in the right eye appeared to have coalesced and developed into early dendrites. At this time she was advised to continue the acyclovir and was also prescribed 0.5% Vigamox every two hours in both eyes.

On 48-hour follow-up she reported improvement in all symptoms. Evaluation of the right eye revealed minimal superior lid edema, reduction in hyperemia of the bulbar and palpebral conjunctiva, and partial resolution of the corneal stellate epithelial lesions. The left eye also revealed resolving stellate epithelial lesions and hyperemia. Due to her improvement the patient was advised to continue with the acyclovir and reduce her Vigamox use to four times a day in both eyes.

By day 25 all epithelial stellate lesions had resolved and only trace superficial punctate keratitis remained in both eyes. At this time the patient was given permission to discontinue the Vigamox and resume contact lens wear, limiting wear time to four to five hours a day.

## **III. Classification of HSV Keratitis**

### **A. Epithelial Keratitis:**

HSV epithelial keratitis accounts for 50-80% of ocular HSV.<sup>7</sup> The earliest manifestation of HSV epithelial keratitis takes the form of small, often raised, intraepithelial vesicles. These vesicles can mimic intraepithelial infiltrates often found in epidemic keratoconjunctivitis or infiltrative keratitis. Herpetic epithelial lesions are predominantly elevated with irregular borders and varying morphology, whereas infiltrates of EKC or infiltrative keratitis are normally flat, pinpoint and round with distinct borders.

After one or two days vesicles may coalesce and develop into linear branching dendrites with raised borders, central ulceration and terminal end bulbs; however, terminal bulbs are not always present. Terminal bulbs, unlike the central ulcer, contain active herpes virus and devitalized cells which therefore stain with Rose Bengal. The base of the central ulcer stains with fluorescein.<sup>5</sup> Only nine to 15% of HSV keratitis presents with dendrites.<sup>4</sup> The presence of a dendrite depends on multiple factors, including the integrity of the corneal epithelium, the duration of the infection, the virulence of the strain and the host's immune status. As the infection progresses, dendrites may evolve into an amorphous geographic ulcer.<sup>5</sup>

#### **B. Neurotrophic Keratitis:**

Five percent of cases of epithelial keratitis will develop into neurotrophic keratitis. Progression to neurotrophic keratitis occurs in the presence of unstable tear film, basement membrane formation or impaired corneal sensitivity.<sup>9</sup> It typically presents as a non-healing, oval epithelial defect with smooth, elevated borders. It is often accompanied by neovascularization, opacification, or various degrees of inflammation and may be complicated by corneal thinning, melting or perforation.<sup>9</sup>

#### **C. Stromal Keratitis:**

Herpetic stromal keratitis can present in one of two forms: 90% immune stromal keratitis (ISK) and 10% necrotizing stromal keratitis (NSK).<sup>10</sup> In both cases, the keratitis may occur with or without the presence of epithelial ulceration.<sup>9</sup>

Immune stromal keratitis may present days or even years after an HSV epithelial keratitis. It is thought to be caused by an inflammatory immune response to retained viral antigen after the virus itself is cleared from the cornea. It presents as focal, multifocal or diffuse stromal infiltrates which can ulcerate over time.<sup>5</sup> Immune rings, neovascularization or ghost vessels may also be present and the condition may be chronic or recurrent. Both NSK and ISK may be further complicated by iritis, trabeculitis, or corneal scarring, although NSK has a much greater propensity to develop corneal thinning, melting or perforation.<sup>5</sup>

#### **D. Endotheliitis:**

Endotheliitis occurs once the virus has spread to the endothelial cells. Persistent endothelial inflammation and subsequent damage to aqueous pumps lead to epithelial edema, stromal edema or even bullae. The endothelial edema may be diffuse, linear or more commonly oval in shape and is normally accompanied by underlying keratic precipitates and iritis.<sup>11</sup>

### **IV. Laterality**

While ocular HSV is thought to be a unilateral condition, the frequency of bilateral ocular HSV varies in the literature. This is in part due to the variability in the definition of bilateral HSV; some report it to be the presence of any form of lid, conjunctival or cornea herpetic disease, and others simply the presence of any form of herpetic keratitis.

Souza, P. et al. reported that 98% of cases of primary HSV infection are unilateral. In their research, 1.3% (7 in 544) of patients presented with bilateral HSV keratitis; however, their criteria for defining bilateral HSV keratitis was not stated.<sup>4</sup> On the other hand, Wilhelmus, K. et al. report a 3% (30 in 1000) incidence of bilateral HSV keratitis. Their diagnosis was solely based upon the presence of characteristic dendritic or geographic ulceration.<sup>7</sup> Darougar, S. et al. report an incidence of 19% (20 in 180) of bilateral HSV. In this case, bilateral HSV is characterized by the presence of any bilateral herpetic lid or corneal lesions and positive identification via immunofluorescent staining technique.<sup>12</sup>

Bilateral HSV appears to be more common in younger patients and those with systemic atopy. The increased susceptibility of atopic or other immunocompromised patients to bilateral HSV is presumed to be due to amplified T-cell destruction in the inflammatory response to the herpes virus.<sup>4,13</sup>

According to Souza, P. et al., the majority of patients with bilateral HSV were of young age, with a mean of 19.3 years. Five of these seven patients were also diagnosed with systemic atopy (compared to 12% according to Wilhelmus, K et al.). There were two cases of severe ocular rosacea, one case of Crohn's disease and ankylosing spondylitis, and one case of systemic lupus erythematosus. In addition, these patients seemed to have an increased rate of recurrence with a total of 44 episodes within 5 years.<sup>4</sup>

In the United States, the seroprevalence of HSV-1 appears to be decreasing, possibly due to improved hygiene and living conditions. The National Health and Nutrition Examination Survey determined that the seroprevalence of HSV-1 from 1999 to 2004 was 57.7%, 6.9% lower from 1988 to 1994.<sup>8</sup> In contrast, the seroprevalence of HSV-2 continues to rise, as it is associated with sexual behavior.<sup>13</sup> Today, approximately one in six persons in the United States are HSV-2 seropositive; a 31% increase over the past 13 years.

In the 1980's, a study out of London, UK, observed a decrease in the rate of primary HSV-1 ocular infection under the age of five from 29% to 7%, whereas young adults showed an increase from 41% to 64%. Increased incidence of primary ocular HSV in young adults may be the result of decreased rates of infection in childhood.<sup>8</sup> A U.S. study determined that positive predictive factors of HSV-1 serology include female gender, African-American race, first intercourse before the age of 15 and partners with oral sores. Positive predictive factors of HSV-2 serology also include female gender and African-American or Hispanic race, in addition to older age, poverty, cocaine use, less education and unprotected sex with multiple partners.<sup>8</sup>

## **V. Management**

Anti-herpetic drugs interfere with viral DNA replication via inhibition of DNA polymerase.<sup>7</sup> The current gold standard for the treatment of primary or recurrent HSV keratitis are topical antivirals, most notably 1%

trifluridine or 0.15% Zirgan gel.<sup>14,15</sup> Topical antivirals may be supplemented by oral antivirals including acyclovir, valacyclovir, or famciclovir.

<b>Dosing Regimens of Antivirals</b>	
<b>TOPICAL ANTIVIRALS</b>	
1% Trifluridine	nine times per day for five to seven days
0.15% Zirgan	five times per day until the epithelial defect has healed, and then three times per day for an additional seven days
<b>ORAL ANTIVIRALS</b>	
Acyclovir	400mg five times a day for seven to 10 days
Valacyclovir	500mg three times a day for seven to 10 days
Famciclovir	250 mg three times a day for seven to 10 days

Although effective, thimerosal-based trifluridine is associated with significant corneal epithelial toxicity and burning or stinging upon instillation (4.6%).<sup>15</sup> The frequent dosing regimen also causes concern with regards to patient compliance. Other reported side effects include palpebral edema, superficial punctate keratopathy, epithelial keratopathy, hypersensitivity, stromal edema, irritation, keratitis sicca, increased hyperemia, and increased intraocular pressure.<sup>15</sup> Although it is generally recommended to limit use of trifluridine to 21 days, toxic reactions can occur as early as five to seven days after initiating treatment.<sup>16</sup> The recently FDA-approved Zirgan gel addresses some of these issues as it is dosed five times a day and has a reduced risk of corneal toxicity. The most common adverse reactions to Zirgan are blurred vision (60%), ocular irritation (20%), superficial punctate keratitis (5%), and conjunctival hyperemia (5%).<sup>14</sup>

It is generally accepted that topical steroids should be avoided in cases of active HSV epithelial keratitis. Topical steroids have been shown to interfere with normal immune defense mechanisms, thus allowing the virus to replicate more rapidly. This prolongs the course and increases the severity of the disease.<sup>17</sup> Complications include enlargement of stellate epithelial or dendritic ulcers, progression to necrotizing stromal keratitis, development of an iritis or hypopyon, or even secondary glaucoma.<sup>17</sup> The mechanism by which these occur however is currently unknown.<sup>18</sup> Studies such as the Herpetic Eye Disease Study, indicate that topical steroids are beneficial in the management of active stromal keratitis and endotheliitis.

The Herpetic Eye Disease Study investigated the role of topical corticosteroids in the treatment of herpes simplex stromal keratitis. Results demonstrated more rapid resolution of stromal keratitis and fewer treatment failures when treated with both prednisolone phosphate and topical trifluridine as opposed to topical trifluridine alone. In addition, delaying the initiation of topical steroid did not appear to affect the resultant visual acuity.<sup>1</sup>

Should both epithelial and stromal keratitis or endotheliitis be present concomitantly, it is recommended that topical steroids be avoided until the majority of the epithelium has healed. When stromal keratitis or endotheliitis occurs in the absence of epithelial disease, topical or oral antivirals should be prescribed as

prophylaxis against reactivation of epithelial disease.<sup>3,9</sup> The Herpetic Eye Disease Study recommends a minimum of four times a day dosing of antiviral medication when steroid treatment is initiated.<sup>1</sup> Steroid treatment should begin with four to eight times a day dosing of 1% prednisolone acetate or phosphate and should be progressively tapered as the cornea heals.<sup>10</sup>

## VI. Discussion

At clinics such as the University of California, Berkeley Tang Eye Center and the University of California, San Francisco Proctor Foundation, treatment of primary or recurrent HSV epithelial keratitis is 800mg acyclovir for 10 days without use of topical antivirals. Although the widely accepted dosage for active HSV keratitis is 400mg five times per day, in our experience 800mg at the same dosage frequency appears to heal the cornea at a faster rate; approximately 50% of herpetic epithelial lesions heal within 24 hours when treated with 800mg of acyclovir, or three to seven days when treated with 400mg of acyclovir. The increased rate of healing with a higher acyclovir dosage is most likely due to absorption of a higher drug concentration into corneal tissue. There may also be the added benefit of increased reduction of viral load in the ciliary ganglion and associated nerves, even if the corneal epithelium is not severely affected.<sup>16</sup> Topical antivirals only treat surface epithelial disease and do not have significant stromal penetration.

Although the bioavailability of oral acyclovir is 15-30%, its distribution volume is around 70%.<sup>19</sup> This ensures a high concentration of the drug in tissues throughout the body, including the eye. With topical 3% ophthalmic acyclovir, tears, aqueous and plasma contain drug concentrations of 1.87 $\mu$ m, 7.5 $\mu$ m and <0.01 $\mu$ m respectively. Four hundred milligrams of acyclovir, on the other hand, produces tissue concentrations of 0.64 $\mu$ m, 3.26 $\mu$ m, and 3.28 $\mu$ m respectively.<sup>19</sup> It is hypothesized that 800mg of oral acyclovir would thus provide even greater corneal penetrance and consequently more rapidly reduce viral load, clinical duration of the infection and risk of stromal involvement.<sup>20</sup> Despite doubling the recommended dosage, acyclovir has very limited side effects. Most common side effects include nausea or vomiting (2.4%), diarrhea (2.7%) and headaches (2.2%) in patients on long-term therapy of over one year.<sup>19, 21</sup> Since acyclovir is metabolized by the kidneys, it is contraindicated in patients with kidney disease.

There is much controversy surrounding whether an oral antiviral should be added to topical antiviral therapy in the management of HSV keratitis. According to the first Herpetic Eye Disease Study (HEDS 1), there is no apparent benefit in the addition of oral acyclovir to corticosteroids and trifluridine in the treatment of HSV stromal keratitis. In addition, according to the second Herpetic Eye Disease Study (HEDS 2), the addition of oral acyclovir to trifluridine in the treatment of HSV epithelial keratitis does not reduce the risk of progression to stromal keratitis or iritis. In fact, treating epithelial keratitis with topical trifluridine alone resulted in a low risk of stromal keratitis or iritis one year following the episode.<sup>22</sup>

To date, there are no established clinical trials investigating the efficacy of topical trifluridine versus oral antiviral monotherapy in the management of HSV epithelial keratitis. Collum. L et al. investigated the efficacy or 3% acyclovir ophthalmic ointment versus 400mg oral acyclovir (both dosed five times daily for a period of 14 days) in the management of simple dendritic herpetic keratitis. No statistically significant difference in the median time to healing was found.<sup>20</sup> There were also no significant side effects reported for either treatment group.

In our experience, patients are more likely to be compliant with oral acyclovir than topical trifluridine based on cost of medication and frequency of dosage. An online search showed that fifty tablets of 800mg generic acyclovir costs between \$25 and \$50. One 7.5mL bottle of 1% trifluridine however costs between \$60 and \$130.<sup>26</sup> Frequency of dosage is also greater with topical trifluridine than oral acyclovir; trifluridine is dosed nine times daily, whereas oral acyclovir is dosed five times daily. Oral acyclovir tends to be more available to consumers as well. Few pharmacies will hold topical trifluridine due to its short shelf life.

In our case, the patient was initially treated with 800mg of acyclovir five times a day. At her 24-hour follow however the patient's symptoms and clinical signs did not improve as anticipated. At this time the patient was prescribed adjunctive Vigamox every 2 hours. Adjunctive treatment with Vigamox is atypical at the UC Berkeley Tang Center. It is reserved for cases of HSV epithelial keratitis that show no improvement in 24 hours after initiating oral acyclovir or used as prophylactic antibiotic treatment when abundant or severe epithelial defects are present.

Research by Bapat, et al. suggests that fluoroquinolone antibiotics may possess antiviral activity. Fluoroquinolones interrupt bacterial DNA replication by directly binding to DNA gyrase and topoisomerase IV; this complex inhibits gyrase and topoisomerase from binding to bacterial chromosomes.<sup>24</sup> Several types of DNA viruses have been shown to also contain various types of topoisomerase enzymes and even share structural similarities with bacterial topoisomerases.<sup>23</sup> Mottola, et. al. investigated the use of fluoroquinolones in interfering with the DNA replication of the African Swine Fever virus (ASFV), a virus that encodes for topoisomerase II. By injecting healthy animal cells with the ASFV and treating them with various concentrations of thirty different quinolones at varying times after infection, they were able to analyze their effect on viral replication, cytotoxicity and protein synthesis.

Mottola also showed that fluoroquinolones dosed at 100µg/mL, such as gatifloxacin (Vigamox), possessed cellular protective effects. Virally infected animal cells treated with fluoroquinolones four hours after infection showed little or no cell degeneration after seven days. Untreated cells demonstrated clear degeneration (i.e. reduced plasma:nucleus ratio and change in normal morphology) twelve hours after viral infection. This suggested a delay in ASFV replication.<sup>23</sup> In addition, inhibition of viral cell infection appeared to occur most during the early stages of fluoroquinolone treatment, suggesting that ASFV topoisomerase II played an importance role in the early phase of viral infection.<sup>23</sup>

The bacteriocidal effects of fluoroquinolones are caused by fragmentation of bacterial DNA via the production of DNA-topoisomerase cleavage complexes.<sup>23</sup> No viral genome fragmentation was observed, in Mottola's study. He proposed that other mechanisms of action took place in which fluoroquinolones interfered with the ATP-ase activity or ATP hydrolysis of ASFV topoisomerase II. Both mechanisms would lead to torsional/replicative stress without breaking the viral chromosome but causing a reduction in viral DNA replication and viral protein synthesis.<sup>23</sup>

The herpes simplex virus is a double-stranded DNA virus.<sup>23</sup> Studies suggest that HSV-1 and HSV-2 use host topoisomerase 1 and 2 in the process of viral replication.<sup>24, 25</sup> It is unclear at this time exactly how these enzymes are involved in the replication of HSV. There is suspicion however that topoisomerase 2 may play a role in cleavage of HSV-1 DNA.<sup>25</sup> While there is still much to learn about herpes simplex viral replication, evidence is

promising that fluoroquinolones may have similar effects on HSV given the parallel topoisomerases as the ASFV. It is hypothesized that fluoroquinolones may temporarily reduce host cell replication in an attempt to allow the patient's own immune system to clear the virus.

## VII. Conclusion

Herpes simplex keratitis is generally accepted to be a unilateral condition in 81 to 98% of cases. The incidence of bilateral HSV keratitis is limited by its definition. Many studies label HSV keratitis as bilateral only if herpetic dendrites or ulcers are visible on both corneas. If the criteria for bilateral HSV keratitis included any form of herpetic keratitis, regardless of severity, its incidence would likely be greater.

Today, one of the standard treatments for HSV epithelial keratitis is 400mg acyclovir five times a day for 10 to 14 days. Dosing at 800mg however may allow more rapid healing as a higher concentration of the drug accesses all layers of the cornea in addition to the aqueous and tear film. Acyclovir is normally well tolerated and produces very limited side effects. Doubling the dosage of acyclovir is unlikely to increase the risk of side effects.

There is some evidence that fluoroquinolones possess anti-viral properties. Further research is needed to determine the mechanism of action of fluoroquinolones when used to treat HSV keratitis. From clinical experience, it appears that Vigamox may be attributed to resolution of HSV keratitis when oral acyclovir monotherapy failed.

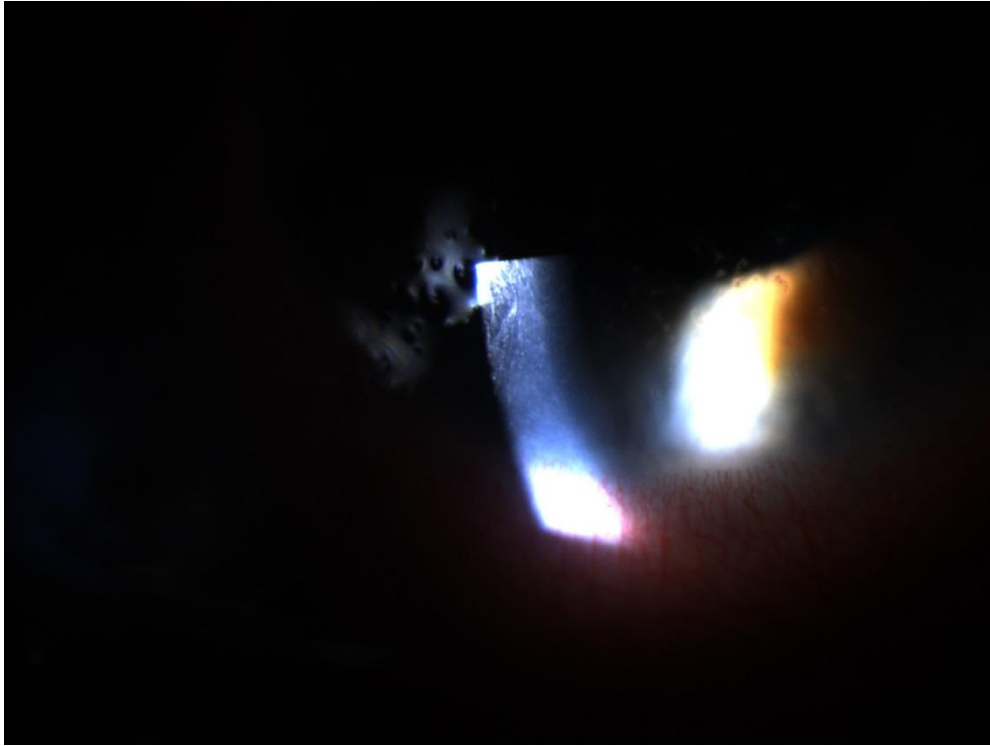
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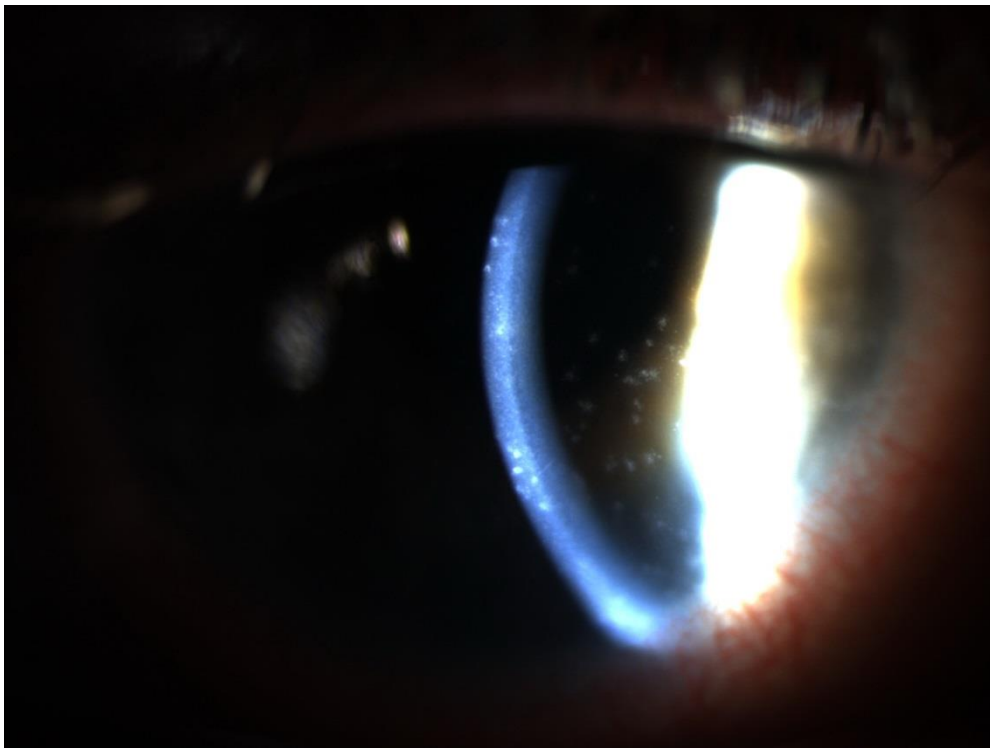


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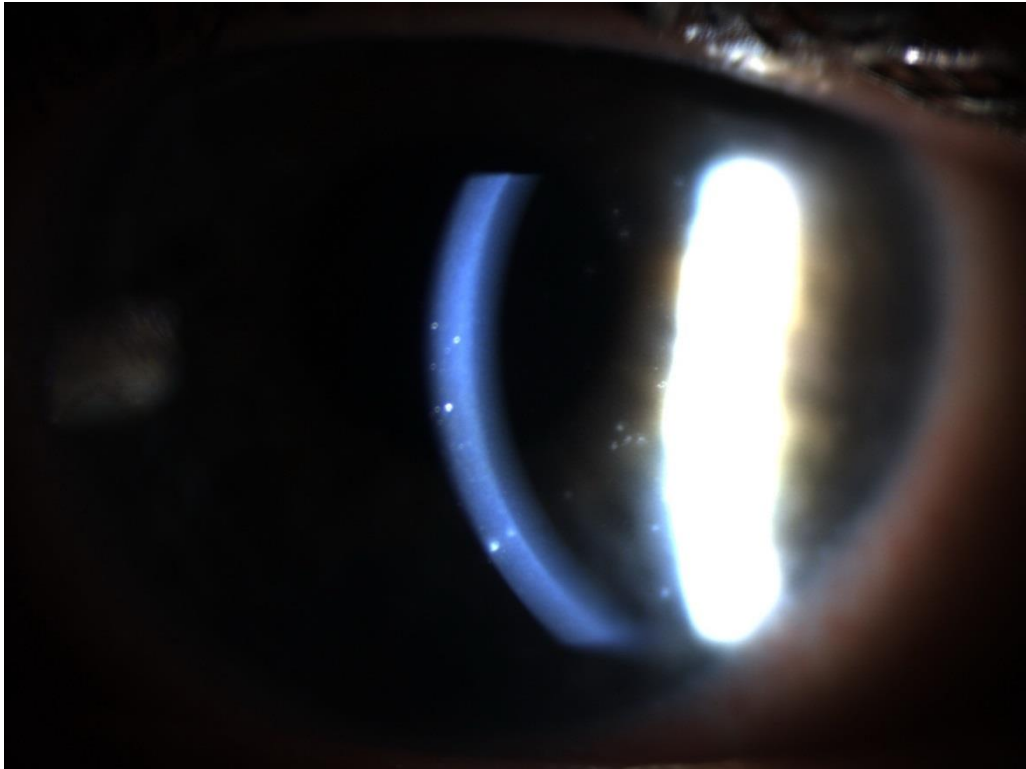
**IX. Addendum**



**Figure 3:** Elevated stellate lesions of HSV epithelial keratitis OD seen on the left in indirect illumination (Day 1)



**Figure 4:** HSV epithelial keratitis OD seen in direct and indirect illumination with white light (Day 1)



**Figure 6:** HSV epithelial keratitis OS seen in direct and indirect illumination with white light (Day 1)