Herpes Simplex Virus Keratitis: A Treatment Guideline

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METHODS AND KEY TO RATINGS

Clinical practice guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network (SIGN)[1] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[2] group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.[3]

♦ All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.

♦ To rate individual studies a scale based on SIGN is used. (Please refer to the bibliography to see the SIGN designations for each cited study.) The definitions and levels of evidence to rate individual studies are as follows:

SIGN[1] Study Rating Scale

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)
III*	Interventional case series

The following studies were not assigned a SIGN Level and were labeled NA: Reviews, Basic Scientific Research, Textbook Chapters, Cost-Effective Analysis, Survey Studies, and Diagnostic Testing.

♦ Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

GRADE[2] Quality Ratings

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

GRADE[2] Key Recommendations for Care

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain – either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

♦ The Findings and Recommendations for Care boxes, located throughout this manuscript, highlight points determined to be of particular importance to vision and quality of life outcomes. A good practice point may emphasize the importance of patient preferences in decision making or feature a practical point for which there is not, nor is there likely to be, any research evidence.[4]

♦ In the process of preparing this document, a detailed literature search of PubMed, EMBASE, and the Cochrane Library for articles in the English language was conducted in November 2010 on the subject herpetic keratitis for years 1966–2010. These searches were augmented by a manual search of literature identified from the reference lists of selected studies included in the literature review. A second and identical search was completed in April 2013 for years 2010–2013. Complete details of the literature search are available in Support Document VI: Literature Search Details.

♦ A systematic review of the search results was conducted using a quality-weighting approach[1a] and study eligibility was determined in a two-step process by the work group at Massachusetts Eye and Ear Infirmary.[5, 6]

[1a] A quality-weighting approach is a more inclusive approach to conducting a systematic review. The quality-weighting approach to a systematic review includes all relevant studies initially and avoids the possibility of selection biases. This approach provides the benefit of a large pool of studies, fuller representation of the available research on a topic, and an opportunity to empirically examine the relationship between methodology and study outcomes. (Lipsey & Wilson, 2001; Moher et al., 1998).

INTRODUCTION

DISEASE DEFINITION

Herpes simplex virus (HSV) keratitis is an infectious disease of the cornea.

ENTITY

Herpes simplex virus keratitis, includes entities with the following ICD-9 and ICD-10 classifications:

- Herpes simplex with ophthalmic complications, unspecified (054.40), (B00.50)
- Dendritic keratitis (054.42), (B00.52)
- Herpes simplex disciform keratitis (054.43), (B00.52)
- Herpes simplex with other ophthalmic complications (054.49), (B00.59)
- Unspecified keratitis (370.9), (H16.9)
- Corneal ulcer, unspecified (370.0), (H16.009)

PATIENT POPULATION

Individuals of all ages who present with symptoms (photophobia, pain, redness, and a clear discharge; those with central lesions also may present with decreased vision) and signs (corneal epithelial and stromal ulcers and infiltrates, corneal edema, keratic precipitates, and anterior chamber inflammation) suggestive of HSV keratitis.[7]

CLINICAL OBJECTIVE

Diagnosis and management of the patient with HSV infection of the cornea.

PURPOSE

Minimize visual loss, relieve pain and discomfort, and minimize structural damage to the cornea associated with HSV keratitis by improving the diagnosis and management of this disease entity.

GOALS

1. Recognize risk factors that may predispose patients to HSV keratitis and increased frequency and/or severity of recurrences.
2. Establish the diagnosis and nomenclature of HSV keratitis, differentiating it from other causes of keratitis to prevent potential sight-threatening sequelae of HSV keratitis
    a. Diagnosis primarily made with a thorough ophthalmic exam
    b. Utilize appropriate diagnostic tests in cases where a definitive diagnosis may be required and cannot be established by the clinical examination
3. Early diagnosis to prevent potential sight-threatening sequelae of HSV keratitis: stromal scarring, astigmatism, neovascularization, ulceration, perforation.
4. Select appropriate therapy in order to:
    a. Relieve pain and discomfort
    b. Prevent corneal complications related to undertreated or untreated inflammation or vision loss, persistent ulceration, stromal scarring, thinning, astigmatism, neovascularization, and lipid deposition
    c. Prevent complications related to the inappropriate treatment of inflammation in the setting of active viral replication

    d. Prevent complications related to prolonged used of topical and systemic antiviral agents
    e. Prevent complications related to prolonged use of topical corticosteroids
5. Prevent reactivation in the cornea: cumulative effects of repeated reactivation may result in scar or perforation.
6. Educate patients and their families about the nature of this condition, treatment options, symptoms, risk factors for recurrence, and the importance of short-term and long-term follow up.

BACKGROUND

EPIDEMIOLOGY

Herpes simplex virus (HSV) is endemic throughout the world and humans are the only known natural reservoir. Studies examining the presence of HSV-1 DNA in the trigeminal ganglia have determined that at least 90% of the world's population is infected with latent HSV-1 by the age of 60.[8-12] However, according to a 2006 survey study, the overall seroprevalence of HSV-1 in the United States has decreased by 7% between 1988 and 2004.[13]

Herpes simplex virus-1 is transmitted primarily through direct contact with infected secretions (i.e., saliva or tears) or lesions. Seroprevalence is likely to be affected by the degree of exposure to these sources of infection, and would therefore be affected by crowding, poor hygiene, and age.[14] Herpes simplex virus seroconversion rates also differ by socioeconomic class. While 30% of children less than 5 years old in lower socioeconomic populations are seropositive for HSV, only 20% of middle class children have seroconverted. Children in the lower socioeconomic populations have a high rate of seroconversion so that 70–80% of children are seropositive by adolescence. Middle class children seem to maintain the same seroconversion rate until the third decade of life at which point the conversion rate increases to 40–60%.[15] More recent data suggests overall seroprevalence of HSV-1 in adolescents (14 to 19 years old), in the USA, is declining, with prevalence of 42.6% in a cohort examined between 1976 and 1980, to 30.1% in a similar cohort examined between 2005 and 2010.[16] In Africa, HSV-1 seroconversion was evident in greater than 80% of the population in nearly every age group except young children.[17]

Herpes simplex virus is a common cause of corneal disease and is the leading infectious cause of corneal blindness among developed nations.[18] We identified seven papers[18-24] from five different countries, estimating the incidence of ocular HSV. Two Danish studies, published in 1970 and 1979 respectively,[21, 22] included only patients with HSV "dendritic keratitis." Other studies with broader inclusion criteria were papers from Croatia,[23] France,[20] the United Kingdom,[24] and three studies from the United States published between 1950 and 2007.[18, 19, 25] Collectively, these studies estimate the incidence of new cases of ocular HSV to range between 5 and 15 new cases per 100,000 population per year.

The three studies from the United States and those from the United Kingdom and France provide additional information. Two well-regarded retrospective cohort studies from Rochester, Minnesota provide us with much of what we now know about the incidence and prevalence of HSV keratitis in the United States.[14, 18, 19] The first study spanned 33 years (1950–1982) and included 122 patients,[18] and the second study spanned 32 years (1976–2007) and included 394

patients.[19] While the first study looks at all patients (treated and untreated), the second study compares patients given oral antiviral prophylaxis to those not provided prophylaxis. Based on the general population of Rochester, Minnesota, the ocular HSV (new case) incidence in the first study (1950–1982)[18] and the second study (1976–2007)[19] were 8.4 and 11.8 cases per 100,000 population per year, respectively. When extrapolating the data from the first study (1950–1982) to U.S. census data in 1985, and the second study (1976–2007) to U.S. census data of 2000, there is an annual incidence of 20,000 and 24,000 new cases in the United States, respectively. The same census data extrapolation was made for incidence of all new and recurrent cases, yielding 48,000 episodes annually for the first study and 58,000 episodes annually in the second study. Extrapolation of the incidence of new and recurrent cases to the July 1, 2011 estimated U.S. population of 311,591,917 (www.census.gov) yields an estimate of 64,499 new and recurrent cases. Based on this data, both incidence and prevalence of ocular HSV appears to be trending upwards.[18, 19]

The prospective study in France sampled 412 ophthalmologists for three months in 2002 and reported 357 cases of HSV keratitis.[20] The French study found a slightly higher incidence of new cases (13.2 cases per 100,000)[20] when compared to the Rochester Minnesota Studies (8.4–11.8 cases per 100,000).[18, 19] Similarly, the overall incidence (new and recurrent episodes) of HSV keratitis in the French study was higher (31.5 cases per 100,000) when compared to the Rochester Minnesota Study (20.7 cases per 100,000).[14, 18-20]

The Herpetic Eye Disease Study (HEDS), performed in the USA, was a multi-armed set of five randomized, placebo-controlled trials designed to determine best treatments and prophylaxis for HSV keratitis and one epidemiologic study that investigated risk factors. Herpes simplex virus epithelial keratitis accounted for 47% of ocular HSV cases in the HEDS trial, compared to 66.1% of ocular HSV cases in the French study.[20, 25] Similarly, HSV stromal keratitis accounted for 16% of ocular HSV cases in the HEDS trial compared to 29.5% in the French study.

The Herpetic Eye Disease Study focused in part on the use of oral acyclovir to prevent HSV epithelial and stromal keratitis and provides valuable epidemiologic data, particularly with regard to recurrence rates.[25, 26] A HEDS multi-center randomized trial enrolled 703 patients with at least one episode of ocular HSV in the previous 12 months and no disease activity within the previous 30 days. Patients received either 400 mg of acyclovir twice daily or placebo. Regardless of symptoms, ocular exams were performed at 1, 3, 6, 9, and 12 months after the start of treatment.[25]

The placebo arm of the HEDS trial yields a cumulative probability of an ocular HSV recurrence of 32% during the 12-month period.[25, 26] Starting with a cohort of patients with a history of some form of ocular HSV, there are differences in "same type" recurrences between HSV stromal keratitis and epithelial keratitis. For example, the rates of HSV epithelial keratitis in patients with a history of ocular HSV other than epithelial keratitis, compared to those with a history of HSV epithelial keratitis, were essentially equal, 12% and 15% respectively. However, the recurrence rates for HSV stromal keratitis were strikingly different; only 3% of patients with a history of ocular HSV, but not stromal keratitis, developed HSV stromal keratitis compared to the 28% of patients with a positive history of HSV stromal keratitis. In addition, the number of recurrences (all types) was strongly associated with the number of past episodes (all types). Thus, a history of HSV stromal keratitis and a high number of previous episodes (any type) increase the risk of

future recurrence. Evidence also exists to suggest that short intervals between attacks tend to be associated with short intervals between future attacks.[27, 28]

Comparisons can be made between the treatment arm of the HEDS trial and the treatment group of the Rochester study (1976–2007). Rates of recurrent epithelial and stromal keratitis were higher in the HEDS trial (9% vs. 5.7% and 14% vs. 11.4%, respectively).[19, 25, 26] The difference could be explained by the two study designs; a randomized clinical trial (HEDS Study) with scheduled visits vs. a retrospective cohort study (Rochester Study). It is possible that since patients in the HEDS trial had frequent visits scheduled over the course of the year, regardless of symptoms, the diagnosis of recurrent herpes simplex keratitis was made in some cases in which either disease was not apparent to the patient, or not of sufficient severity for patients to seek eye care. Most stromal keratitis recurrences in the HEDS prophylaxis trial were identified during scheduled study visits, rather than on urgent, unscheduled visits.

Finally, ocular HSV and HSV keratitis in particular, represent a significant global burden of disease. Herpes simplex virus keratitis is potentially blinding, requires frequent visits to the ophthalmologist, and is responsible for a significant loss of work and productivity. When permanent, corneal damage from ocular HSV may require surgical intervention and results in over 1,000 penetrating keratoplasties annually in the United States.[29] Between 1987 and 1991 in the United Kingdom, HSV keratitis was responsible for approximately 10% of all corneal transplants.[30]

Globally it is estimated that there are 1,000,000 new cases and 9,000,000 recurrent episodes of ocular HSV each year. It is also estimated that ocular HSV is responsible for visual disability in 1,000,000 people world-wide each year.[31, 32] In the United States, patients make an average of four visits to an ophthalmologist for the first episode and six visits for recurring episodes of ocular HSV.[18] It is estimated that a doctor's visit for ocular HSV results in a loss of one full day of work or leisure per visit.[33] Based on this data and estimates of incidence in the U.S.,[19] an estimated 58 million days of work (444,000 in the U.S.) are lost treating ocular HSV worldwide each year. In addition, there is a significant burden attributed to the disease itself. The mean time from onset of symptoms to resolution of active ocular HSV disease was estimated at 17.6 days for the first episode and 28.4 days for recurrent episodes.[18]

NATURAL HISTORY

Initial Infection

Herpes simplex virus is typically spread by direct contact, most often from virus shed into saliva or genital secretions**.** Herpes simplex virus can be acquired following contact with an active oro-labial lesion. Asymptomatic individuals regularly shed HSV in their saliva,[34] and therefore, HSV can also be acquired by contact with virus-laden saliva of asymptomatic patients.[34] While symptomatic patients shed more HSV viral DNA than asymptomatic patients, the asymptomatic patients are likely the more common source of transmission since there are many more of them.[14]

At the time of initial acquisition of HSV-1, active viral replication in mucosa or skin spreads through neurons to dorsal root ganglia, or in the face, the trigeminal ganglia. Some patients may experience symptoms during this initial acute infection but most patients do not. In fact, nearly two-thirds of all primary HSV infections are either unrecognized or asymptomatic.[35] The first presentation of ocular HSV (which may or may not represent primary infection by the virus) was

elucidated in a study at Moorfields Hospital in London.[24] Between 1973 and 1980, 108 adult patients with primary ocular HSV were studied. This study found that 84% of patients had moderate to severe conjunctivitis, 38% had moderate to severe blepharitis, 35% had a concomitant upper respiratory infection, and 31% had generalized symptoms. Only 15% of these patients had dendritic ulcers and 2% had "disciform keratitis".[24] Twenty (19%) of these patients had bilateral disease.[24]

While it is true that HSV-1 tends to be responsible for most orofacial infections and HSV-2 is responsible for most genital herpes infections, HSV-1 and HSV-2 are found in equal numbers in the trigeminal and sacral ganglia at autopsy.[36] Therefore, local host factors are likely responsible for the predilection of HSV-1 infection for the facial area and HSV-2 for the genital area. The frequency of HSV-2 infections of the orofacial and ocular areas is not well defined. However, HSV-1 disease tends to recur more readily in the orofacial area and less in the genital area after primary infection from either site.[30, 37-39]

Viral Reactivation and Shedding

1. Transmission

Herpes simplex virus is typically infectious during the 5–10 days it takes to heal skin lesions as well as during asymptomatic shedding in saliva.[34] In 2005, Kaufman et al used a quantitative PCR technique to detect HSV-1 DNA in the tears and saliva of 50 asymptomatic HSV-infected patients. Samples were taken twice daily for 30 days, yielding 2,806 samples.[34] The results showed that 33.5% of all samples (941/2,806) contained HSV-1 DNA and 98% of subjects (49/50) shed HSV-1 DNA from their tears or saliva at least once over the 30-day sampling period. Forty-six (92%) subjects excreted HSV-1 DNA in their tears at some time during the study. Only 37 out of 50 (74%) subjects were IgG positive for HSV-1, suggesting that seronegative individuals might still harbor HSV in the trigeminal and/or dorsal root ganglia.

2. Clinical Recurrences

The critical relationship between latency, reactivation, and recurrence has been studied for years, but remains largely elusive. In one hypothesis, both a high number of latent virus copies and the number of latently infected neurons may promote reactivation by overwhelming the cellular mechanisms that silence virus transcription.[40] Recurrence of HSV epithelial keratitis may correlate to trigeminal ganglia reactivation, but the relationship between HSV reactivation in the trigeminal ganglia with recurrences of HSV stromal or endothelial keratitis is not known.

Virus reactivation and shedding in the orofacial area can lead to clinically evident infection of the skin (vesicular dermatitis), ocular surface (conjunctivitis and epithelial keratitis), or asymptomatic shedding only. Compared to primary ocular herpetic disease, which primarily manifests as blepharitis, conjunctivitis, and less commonly HSV keratitis (17%), recurrent disease can manifest as either adnexal infection or HSV keratitis.[18, 24, 25] Most recurrences in the HEDS prevention trial manifested in the cornea (37% epithelial and 46% stromal) as opposed to the eyelid and adnexa, but patients entering the study were selected for a history of HSV keratitis.[25] Recurrent episodes of HSV keratitis account for most of the morbidity associated with ocular HSV. For example, HSV stromal keratitis recurrence, an immunopathologic process, can lead to stromal scarring, neovascularization, endothelial dysfunction, and vision loss.

CLINICAL MANIFESTATIONS AND CLASSIFICATION

It is axiomatic that the proper classification of any illness is critical to proper therapy. The aims of any disease classification system for a multifaceted disorder should be to clearly characterize unique disease forms in a fashion that makes classification easy for the health care provider and leads directly to an evidence-based treatment algorithm. Problems arise in designing and implementing evidence-based treatment algorithms for any group of related disorders when imprecise or confusing terminology is used to characterize or classify the different forms.

Herpes simplex virus keratitis has multiple manifestations. The distinctive nature of these manifestations can be readily distinguished upon careful examination for involvement of the individual layers of the cornea (epithelium, stroma, and endothelium). Data also suggest that HSV keratitis affecting different corneal layers has functionally distinct mechanisms of pathogenesis. For example, HSV dendritic epithelial keratitis occurs due to direct infection of corneal epithelial cells, while HSV stromal keratitis is primarily attributed to immune mechanisms. Herpes simplex virus dendritic epithelial keratitis requires antiviral therapy, while HSV stromal keratitis typically requires a combination of antiviral and topical corticosteroid therapy.

The rational and proper choice of therapeutic intervention in a patient with HSV keratitis is critically dependent on proper characterization of the keratitis. Some terms used to categorize HSV keratitis are poorly and/or incompletely descriptive. For example, "immune stromal," "necrotizing," and "disciform" appear commonly in the published literature and in ophthalmologists' vernacular to describe HSV keratitis,[41, 42] but are problematic. Use of "immune stromal" keratitis implies that other forms of HSV stromal keratitis do not involve the immune system. All forms of stromal keratitis are immune mediated to some degree. Similarly, a cornea believed to have HSV necrotizing keratitis may not always exhibit actual necrosis. Herpes simplex virus disciform keratitis as a description for endothelial keratitis fails to account for cases in which the entire corneal endothelium is involved, i.e., when the involvement is diffuse. Disciform keratitis is also sometimes classified as a subset of stromal keratitis, and the term may be similarly misapplied when HSV stromal keratitis presents with a round or oval stromal infiltrate. To complicate matters, the diagnosis of HSV keratitis is almost always made solely on the clinical appearance of the cornea. Herpes simplex virus infection of the corneal epithelium can be proven by culture, PCR, and other tests, but testing is often too cumbersome, expensive, and the results too delayed to be practical. Office-based diagnostic tests for HSV keratitis involving the corneal stroma and endothelium do not exist.

A simple classification system for HSV keratitis based on anatomical localization of the principal site of corneal involvement directly addresses the need for consistent and easily applicable descriptors of the disorder (Table 1). For example, HSV dendritic and HSV geographic keratitis are both categorized as HSV epithelial keratitis because both represent epithelial infection by HSV and respond to the identical antiviral therapies. Stromal involvement by HSV can be differentiated from epithelial and endothelial forms by slit-lamp biomicroscopy. The use of fluorescein dye will differentiate stromal keratitis with epithelial ulceration from that without ulceration. This simple test informs the practitioner how to balance antiviral and topical corticosteroid therapy. The presence of stromal and epithelial edema with inflammation at the level of the corneal endothelium, signified by keratic precipitates in the absence of significant anterior uveitis, is classified as endothelial keratitis and responds rapidly to the proper

combination of antiviral and topical corticosteroid therapy.

Table 1. HSV KERATITIS: CLASSIFICATION

Corneal Layer	Nomenclature	Alternate Terms
Epithelium	HSV epithelial keratitis	Dendritic epithelial ulcer
		Geographic epithelial ulcer
Stroma	HSV stromal keratitis without ulceration	Non-necrotizing keratitis Interstitial keratitis Immune stromal keratitis
	HSV stromal keratitis with ulceration	Necrotizing keratitis
Endothelium	HSV endothelial keratitis	Disciform keratitis

DISEASE MODIFIERS

The severity and likelihood of recurrent HSV-1 ocular disease may be determined by the virulence of the infecting virus strain, the general susceptibility of the host to herpes virus infections and more specifically to the particular infecting strain, and the local susceptibility of the host target tissue.

HSV Virulence

Research investigations in laboratory animals have shown that different HSV-1 strains vary widely in their capacity to induce disease, although these studies have not been translated to human patients. Little is known therefore about HSV strain differences in the propensity to cause severe and/or recurrent human disease.

General Susceptibility of the Host

The general susceptibility of the host to ocular HSV infections depends on the overall status of the host immune system. Various conditions, inherited or acquired, and age of the affected individual, can reduce the immune system's effectiveness in preventing ocular HSV recurrences. Individuals may experience more severe disease or more frequent recurrences of HSV keratitis because that individual's immune response to viral infections, or more specifically to HSV, is compromised.

Any condition that depresses cell mediated immunity may increase the risk of HSV disease.[43] The published literature suggests that individuals with depressed cell mediated immunity, for example, those after organ transplant,[44-49] or with diabetes mellitus,[50-52] measles,[53-56] or HIV,[57, 58] may experience more severe disease or more frequent recurrences of HSV keratitis.

1. Organ Transplant Recipient

Organ transplant recipients are typically immune compromised due to corticosteroids or other immune suppressant medications, and therefore more susceptible to HSV infection and reactivation. Several case series support an association between immune suppression after organ transplant and recurrence of ocular HSV.[44-49]

2. Diabetes Mellitus

Patients with long-standing diabetes mellitus are thought to have impaired cell mediated immunity.[50, 51] In one retrospective cohort study from Israel, herpetic eye disease was more

commo n in patients with diabetes mellitus, especially those with poor glycemic control, when compared to patients without diabetes.[52]

3. Measles Infection

The measles virus suppresses cell mediated immunity by interfering with T-cell and dendritic cell function.[54] Patients with an acute measles infection are at risk for secondary infections, including HSV. Several cases series have found that patients with measles infection are more likely to develop ocular HSV infection.[53, 55, 56]

4. HIV Infection

Although HSV can be an AIDS-defining opportunistic infection, the incidence of HSV keratitis is no higher in HIV-positive than in HIV-negative individuals.[57] One case series of six patients concluded that patients with AIDS were more likely to have peripheral HSV epithelial keratitis, and require a longer treatment course with topical antiviral therapy, when compared to immunocompetent patients.[58] However, in a retrospective cohort study in San Francisco of patient visits between 1984 and 1994, HIV-positive patients had a higher recurrence rate, but had similar lesion types (epithelial vs. stromal), required similar length of treatment, and similar time to first recurrence when compared to HIV-negative patients.[57]

Altered or Stressed Immune System

Age impacts immune system function, with generally more robust immune responses to infection in children. Also, other external and internal conditions may influence immune system function. For example, atopy may result in an atypical course or presentation of HSV keratitis. The immune system may also be stressed by infection and fever, psychological or emotional stress, menstruation, and even severe weather.

1. Children

Two epidemiologic studies in the U.K. indicate that HSV-1 infections in children and young adults may be declining. In 1967, children accounted for 29%[59] of primary ocular HSV cases. In 1985, children accounted for only 7% of primary cases.[24] Similarly, adolescents accounted for 64%[59] of primary ocular HSV cases in 1967, but 41%[24] of cases in 1985.

Compared to adults with HSV keratitis, children tend to have more severe disease, more recurrences, and more secondary corneal scarring and astigmatism, leading to greater reduction of vision.[60-63] In a retrospective study of 23 children with HSV keratitis, all children had HSV epithelial keratitis, and 60% had both HSV epithelial and stromal keratitis. None had HSV stromal keratitis alone.[60] In a more recent retrospective case series of 57 children (16 years of age or younger) with ocular HSV (in which the authors considered stromal keratitis and disciform keratitis as one entity), 74% of all patients had HSV stromal keratitis with or without another form of ocular HSV and about half of these had stromal disease alone.[63] In contrast, the HEDS prevention trial found only 32% of adult patients had a history of both HSV epithelial and stromal keratitis and 16% of patients had a history of HSV stromal keratitis without epithelial keratitis.[25] Possibly because of difficulty in examining children, HSV keratitis in children is commonly misdiagnosed and may delay treatment for as long as years in some instances.[63]

Children are more likely to experience bilateral HSV keratitis with rates of 3.4–26%,[60-62, 64] compared to 1.3–12% in adults.[14, 65-67]The recurrence rate of HSV keratitis within the first year

of an episode also seems to be higher in children (45–50%)[60, 62, 63] when compared to adults (18%).[68]

Herpes simplex virus stromal keratitis poses a particular problem for children. The inflammatory response in children appears to be more severe, resulting in increased stromal scarring, corneal opacification, and irregular astigmatism.[60, 62, 63] Therefore, young children with HSV keratitis are at risk of developing amblyopia.[60, 62]

When compared to adults, children appear more likely to have bilateral disease, combined HSV epithelial and stromal keratitis, a higher recurrence rate in the first year after an episode, and are commonly misdiagnosed. Children have a more robust inflammatory response during HSV stromal keratitis and may develop corneal scarring that can interfere with vision. Thus, young children with HSV keratitis are predisposed to amblyopia and require closer and more frequent monitoring than adults. *(Strong Recommendation, Moderate Quality)*

2. Atopy and Bilateral Disease

Herpes simplex virus keratitis is typically unilateral, but some patients have bilateral disease. Between 7.5–19% of patients with general ocular HSV have bilateral disease.[18, 24, 63, 67] Between 1.3–12% of adults with HSV keratitis have bilateral disease,[14, 65-67] while 3.4–26% of children with HSV keratitis have bilateral disease.[60-62, 64] Bilateral ocular HSV is more common in primary than recurrent ocular HSV infection. Bilateral ocular disease accounted for 19% of the primary ocular HSV cases in a Moorfields Eye Hospital study of 108 patients.[24] Patients with bilateral herpetic eye disease also tend to have a high proportion of subsequent complications.[66] The reasons for bilateral HSV ocular disease in specific patients is unclear. However, patients with atopy[18, 28, 66] and younger patients[21, 60, 61, 64] are more likely to experience bilateral disease, suggesting host factors determine bilaterality of infection.

The term atopy designates a group of patients with a personal or family history of one or more of the following diseases: hay fever, asthma, and atopic eczema.[69] Atopic patients have altered reactivity to common environmental antigens that do not cause clinical reactions in most people. Atopy is characterized by the persistence or aberrant activation of T_H2 lymphocytes leading to the generation of cytokines that stimulate B-lymphocyte synthesis of IgE antibody and the production of eosinophils.[70] There is a relative imbalance of Th1 and Th2 T-cell immune response in atopic individuals. As a result, atopic patients exhibit altered cell-mediated immunity and are particularly susceptible to HSV infections, including HSV keratitis.[28, 66, 71-74] In a large retrospective case control study in California, individuals with severe atopic disease had between 2.0 and 4.8-fold greater odds of developing ocular HSV than those without atopy.[28]

Patients with atopy have also been noted to have unusually severe HSV keratitis,[66, 71, 72] are more likely to exhibit bilateral disease,[66, 71, 72, 74] and generally show less therapeutic response to topical antiviral agents than with oral agents.[66, 71-73] Atopic patients treated with topical antiviral agents for ocular HSV infection may require prolonged treatment.[71] In contrast, three atopic patients with disseminated HSV and severe ocular involvement were reported to experience clinical resolution with systemic acyclovir within 48 to 72 hours of initiation of treatment.[66, 73]

The prevalence of atopic disease in developed countries has increased substantially over the last few decades.[75] Increased exposure to pollutants and indoor allergens (especially house dust

mites), a decline in breast-feeding, and an increased awareness of atopic disease, have each been suggested as possible contributing factors to increased atopy in the population.[76] As the prevalence of atopy rises, the clinical picture and treatment algorithm of HSV keratitis may also need to change.

Herpes simplex virus keratitis is typically unilateral, and patients with bilateral involvement are often misdiagnosed. It is important to elicit a history of atopic disease in patients with especially severe disease, bilateral disease, or disease recalcitrant to topical antiviral therapy. *(Strong Recommendation, Moderate Quality)*

3. Immune Stressors

Multiple immune stressors have been suggested as triggers of recurrent orofacial and genital HSV, including fever,[77, 78] menstruation,[79] psychological stress,[80-87] and upper respiratory infection.[88] In the HEDS acyclovir prevention trial,[68] the authors concluded that neither gender, ethnicity, age, or a history of non-ocular HSV disease increased the risk of ocular HSV recurrences. There are a limited number of studies looking specifically at immune stressors and ocular HSV disease and recurrence. A HEDS study designed to analyze the relationship between potential external triggers and HSV ocular infection enrolled 308 patients (155 patients in the acyclovir treatment group and 153 in the placebo) who were required to submit a weekly log of personal experiences.[89] Of 308 participants, 67 experienced recurrences, and of these, only 35 submitted a valid weekly log. The study concluded "with reasonable certainty that high stress is unlikely to be associated with activation of HSV eye disease."[89] None of the 35 participants with a valid weekly log reported high stress prior to an ocular HSV recurrence.[89] Known triggers of labial HSV-1 reactivation, such as ultraviolet light exposure[90] and systemic infection, were not associated with recurrent HSV keratitis in this study.[89] The HEDS investigators found that logs completed after ocular HSV symptoms began showed a relatively high degree of stress and systemic infection. Aside from the HEDS trial, the remaining published literature on immune stressors and ocular HSV is limited to small case reports/series.

Local Susceptibility of Host Tissue

The cornea may be more susceptible to HSV keratitis under certain conditions, including administration of local and systemic medications, trauma, and local inflammation due to other causes. In some cases, a combination of trauma, inflammation, and subsequent treatment with topical corticosteroids may increase susceptibility to HSV keratitis.

1. Topical Medications

Host tissue (cornea) may become more susceptible to HSV infection and recurrence with topically, intravitreal, or systemic medications. In humans, recurrent ocular HSV-1 disease has been attributed most to use of prostaglandin agonists, corticosteroids, and inhibitors of angiogenesis.

a. Prostaglandin Analogs

Prostaglandin analogs are topical ocular hypotensive agents for the treatment of elevated intraocular pressure. Prostaglandins also mediate inflammation by activating adenylate cyclase, which increases intracellular cAMP that then binds to protein kinase A, resulting in the phosphorylation (and activation) of transcription factors. Cases of HSV epithelial keratitis coincident to administration of latanoprost have been reported.[91-93] Patients presented with HSV

epithelial keratitis, often bilateral, within three months of starting the drug. When the latanoprost was stopped, the epithelial keratitis resolved. If the drug was restarted, epithelial keratitis reappeared. Some of the reported patients had no clinical history of ocular HSV. It may be advisable to avoid topical prostaglandin analogs in patients with a known history of HSV.

b. Corticosteroids

Corticosteroids are potent anti-inflammatory mediators and affect virtually every aspect of the immune response.[94] In cell culture models, corticosteroids also appear to have a direct effect on reactivation of latent virus.[95] The topical, intravitreal, and/or systemic use of corticosteroids can predispose to severe HSV epithelial keratitis. In one double blind placebo controlled study of 50 patients at Moorfields Eye Hospital, 42% of patients with HSV stromal keratitis treated with topical corticosteroids and placebo developed HSV epithelial keratitis compared to 15 percent of the patients treated with topical corticosteroids and an antiviral agent.[59] In another randomized trial, 56 patients with herpetic keratouveitis and no signs of HSV epithelial keratitis were treated with topical corticosteroids and either topical trifluridine or placebo.[96] This study found that 21% of the patients assigned to placebo and no patients assigned to treatment with trifluridine developed HSV epithelial keratitis during the treatment period.[96] Several case series also implicate topical[97, 98] and intravitreal[99] corticosteroids as a trigger for HSV epithelial keratitis.

c. Angiogenesis Inhibitors

Bevacizumab (Avastin®; Genentech, San Francisco) and ranibizumab (Lucentis®; Genentech, San Francisco) are humanized monoclonal antibodies to vascular endothelium growth factor used to treat the neovascular form of macular degeneration. Recently, there has been interest in the use of bevacizumab and ranibizumab for the treatment of corneal neovascularization,[100-106] including corneal neovascularization caused by herpetic stromal keratitis.[102-104, 107] There are several case reports demonstrating the safety and efficacy of angiogenesis inhibitors for the treatment of corneal neovascularization in the literature. One case report describes the beneficial effect of bevacizumab in a patient with corneal neovascularization after HSV keratitis.[107] One case report described HSV epithelial keratitis three days following intravitreal injection of bevacizumab.[108] The relationship between administration of the angiogenesis inhibitor and HSV keratitis remains unconfirmed.

2. Local Trauma and Inflammation

a. Contact Lens Wear

The HEDS study on the potential triggers of HSV keratitis[89] determined that there was no association between contact lens wear and HSV recurrences. In a separate case control study, 42 patients with HSV keratitis were compared to control subjects to assess the prevalence of a variety of risk factors, including contact lens wear.[109] This study also found no association between contact lens wear and HSV keratitis. In contrast to these two studies, a retrospective cohort study found an increased risk of recurrence of HSV keratitis in 21 contact lens wearers as compared to 96 non-contact lens wearers.[110] However, one could argue that patients wearing a contact lens might be those with more severe prior disease and thus more likely to recur. The authors also could not control for use of antiviral prophylaxis in their patient groups.

b. Laser Surgery

The pathogenesis of HSV keratitis following local laser procedures remains controversial. Possible explanations for laser surgery inducement of HSV keratitis include focal laser trauma to

corneal nerves and/or the cornea itself with secondary inflammation, a direct activating effect of laser light, and postoperative corticosteroid use. There are several case reports/series in the literature of HSV keratitis following ocular laser procedures, including laser assisted in situ keratomileusis (LASIK), laser iridotomy, laser trabeculoplasty, and therapeutic laser keratectomy.

(i) LASIK

There are seven case reports/series totaling nine patients reporting HSV keratitis in the early postoperative period after LASIK.[111-117] Recurrent HSV epithelial keratitis generally occurred on the first postoperative day.[113, 114] Herpes simplex virus stromal keratitis generally occurred several weeks after LASIK.[111, 116] Three interventional case series including 36 patients with a history of HSV epithelial keratitis suggested that oral antiviral prophylaxis is effective in preventing recurrences of HSV keratitis.[118-120] There are no prophylactic studies looking specifically at HSV stromal keratitis after LASIK, but LASIK may be inadvisable in patients with a history of HSV stromal keratitis. In patients immediately post-LASIK, who present with HSV epithelial keratitis, corticosteroids should be tapered as is feasible while managing the keratitis with antiviral therapy. In patients with a known history of ocular HSV, ideally oral antiviral agents should be started prior to the procedure and continued through the immediate postoperative period.[113]

(ii) YAG Laser Iridotomy and Capsulotomy

Laser iridotomy is used to prevent and treat angle closure glaucoma. Both YAG and argon lasers are used in laser iridotomy procedures. While the total energy for laser iridotomy is relatively low, corneal damage has been documented.[121-124] There are two case reports of recurrent HSV keratitis following laser iridotomy.[125, 126] Since most patients treated with laser iridotomy receive post-procedure corticosteroids, it is unclear if the HSV recurrences were directly related to the laser treatment or the corticosteroids.

(iii) Argon Laser Trabeculoplasty

Argon laser trabeculoplasty is sometimes used in the management of open angle glaucoma. One case of HSV keratitis recurrence after argon laser trabeculoplasty has been reported.[127]

(iv) Phototherapeutic/Photorefractive Keratectomy

Excimer laser phototherapeutic keratectomy has emerged as an alternative therapy to lamellar or full thickness corneal transplantation for the treatment of multiple corneal diseases, including superficial scars and surface irregularities from HSV keratitis. Positive outcomes have been reported,[128] but several case reports also describe post-procedure recurrences of HSV keratitis after excimer laser surface ablation.[117, 128-134] In a case series of 20 patients with a history of HSV keratitis, 25% of patients experienced a recurrence during the 17-month, follow-up period.[128] Similar case reports of HSV keratitis recurrences after photorefractive keratectomy have been reported.[128, 135-137] One retrospective chart review of 13,200 patients with no history of HSV keratitis reported 19 cases of HSV keratitis immediately following the procedure.[138]

c. Surgery

Performing surgery of any kind on an eye with a history of HSV ocular disease raises the potential for viral reactivation. The trauma from the surgery as well as local immunosuppression caused by the routine use of perioperative corticosteroids may trigger or worsen recurrent HSV

keratitis. Antiviral prophylaxis should be strongly considered for all patients with a history of HSV ocular disease in the immediate perioperative period, especially while under treatment with corticosteroids.

(i) Cataract Surgery

There are several case reports of HSV epithelial keratitis within the first postoperative week after phacoemulsification surgery.[139-141] It is unclear what role topical corticosteroids may have played in these cases. Most of these cases were in patients with no documented history of HSV keratitis.[139, 140]

(ii) Penetrating or Lamellar Keratoplasty

The two principal reasons for graft failure following penetrating keratoplasty in patients with herpetic eye disease are viral reactivation, resulting in clinical recurrence of herpetic disease, and simple allograft rejection.[142-144] The etiology of HSV keratitis recurrence after penetrating keratoplasty is controversial, but involves reactivation of latent HSV-1 in the host trigeminal ganglion, or transmission from subclinical infection of the donor cornea.[145-150] Also, HSV recurrences appear to increase the risk of graft rejection and subsequent graft failure.[30] Compared to patients without a history of HSV ocular infection, patients with a history of ocular HSV have a higher incidence of allograft rejection.[151]

Following penetrating keratoplasty, the recurrence rate of HSV keratitis in patients without oral antiviral prophylaxis was reported as 32% at four months,[152] 44% at 21 months,[153, 154] 39–46% at one year,[145, 155] and 27–50% at two years[156, 157] postoperative. Several studies have concluded that corneal transplant patients with a known history of HSV keratitis treated prophylactically with systemic acyclovir have fewer recurrences of HSV keratitis when compared to those who have not been treated with systemic acyclovir.[153-161] These studies include one randomized placebo-controlled trial with a five-year follow up,[157, 162] four small randomized non-placebo-controlled trials,[153, 154, 156, 160] and four retrospective cohort studies.[155, 158, 161, 163]

The recurrence rate of HSV keratitis following penetrating keratoplasty seems to be inversely related to the length of treatment with oral acyclovir. One year post keratoplasty, the recurrence rate in patients treated with oral acyclovir for three weeks is 30%,[160] for three months, 18%,[155] for six months, 5.7%,[157] and for one year between 0 and 5%.[153, 154, 160] While the recurrence rates in the groups treated for six months versus one year are similar, there may be an advantage to treating patients for at least a full year with prophylactic oral antivirals since most recurrences of HSV keratitis occur in the first year after keratoplasty.[30, 145, 152-155, 158, 164, 165] Furthermore, patients treated with oral acyclovir for one year had reported HSV keratitis recurrence rates of 0% at 16 months,[153, 154] and 5% at two years[160] from the start of treatment. This compares to a 27–50% recurrence rate for ocular HSV, two years following penetrating keratoplasty in patients that were not treated with antiviral prophylaxis.[157, 166] Further, it appears reasonable following keratoplasty to continue prophylaxis with oral antivirals for as long as the patient remains on topical corticosteroids.

Several studies on deep anterior lamellar keratoplasty (DALK) in patients with post-HSV stromal scarring showed improved visual outcomes and similar recurrence rates (0–33% at one year) relative to prior studies on patients receiving penetrating keratoplasty for the same indication, when also using oral antiviral prophylaxis after surgery.[167-171]

PREVENTION AND EARLY DETECTION

Recurrent HSV stromal keratitis can be associated with permanent vision loss due to corneal scarring and astigmatism. Therefore, prevention of HSV keratitis in patients who experience multiple recurrences is an important goal. Published randomized, double-masked and placebo-controlled clinical trials for HSV keratitis prophylaxis include studies of low-dose/long-term oral antiviral prophylaxis,[25, 26] high-dose/short-term oral antiviral prophylaxis,[172] and comparison of oral acyclovir and its prodrug, valacyclovir,[173] in the prevention of HSV keratitis.

The first clinical trial, conducted by the HEDS group, recruited 703 immunocompetent patients who had experienced an ocular HSV episode in the previous year.[25, 26] These studies investigated the efficacy of oral acyclovir (400 mg bid) versus placebo in preventing ocular HSV recurrences in patients with a history of ocular HSV over 12 months[25] and 18 months.[26] During the 12-month treatment period, patients treated with oral acyclovir experienced approximately half as many recurrences of ocular HSV as the placebo group. There was no statistical difference in recurrences between the two groups in the six months after cessation of treatment, suggesting the absence of a prolonged effect of acyclovir prophylaxis once off the medication. A subgroup analysis[25] concluded that 12 months of oral antiviral prophylaxis is effective in preventing both HSV epithelial and stromal keratitis. The benefit of preventing HSV stromal keratitis, however, was only significant in patients with a history of HSV stromal keratitis. Among patients with a history of HSV stromal keratitis only 14% experienced recurrences compared to 28% in the placebo group. Among patients with a history of ocular HSV other than stromal keratitis, 4% developed HSV stromal keratitis compared to 3% in the placebo group. Overall, the greatest benefit of oral antiviral prophylaxis was seen in patients with a history of HSV stromal keratitis and those with history of multiple recurrences of any type of ocular HSV.

The majority of morbidity associated with ocular HSV is due to HSV stromal keratitis. Therefore, a long-term (one year or greater), low-dose oral antiviral prophylaxis is recommended for patients with a history of recurrent HSV stromal keratitis. See Appendix VI for treatment options and dosing. *(Strong Recommendation, Good Quality)*

A second clinical trial conducted by the HEDS group investigated the efficacy of short-term/high-dose oral antiviral in preventing HSV stromal keratitis recurrences over 12 months in patients with active HSV epithelial keratitis at the time of enrollment. This study enrolled 287 patients who were being treated for HSV epithelial keratitis with topical trifluridine solution.[172] Study subjects were also treated with either oral acyclovir 400 mg five times daily for three weeks, or placebo. The addition of high dose oral antiviral agents to topical antiviral agents for three weeks in patients with HSV epithelial keratitis had no benefit in preventing future episodes of HSV stromal keratitis. The results of this study were consistent with previous HEDS data showing that patients with a history of ocular HSV not affecting the corneal stroma rarely experience episodes of HSV stromal keratitis later.[25, 26]

In another randomized, but unmasked clinical trial of 52 patients with a history of recurrent ocular HSV, the efficacy of oral acyclovir was compared to oral valacyclovir in the prevention of ocular HSV recurrences.[173] Patients were treated with either 400 mg acyclovir twice daily or

valacyclovir 500 mg once daily for 12 months. The recurrence rates of ocular HSV in both groups were 23.1%. This study concluded that valacyclovir was as effective as acyclovir at preventing ocular HSV recurrences in patients with a history of ocular HSV. There were no serious adverse effects reported in either group and none of the patients in this study discontinued the drug from intolerance.

Long-term (one year), low-dose antiviral agents (acyclovir 400 mg twice daily or valacyclovir 500 mg once daily) are the only antiviral agents proven to reduce the incidence of recurrent HSV keratitis. While there are no clinical trials investigating the effect of famciclovir on the treatment and prevention of HSV keratitis, it is reasonable to extrapolate from existing genital herpes recurrence studies as well as the ocular penetration studies[174] to suggest famciclovir 250 mg twice daily as an acceptable alternative to acyclovir or valacyclovir for prophylaxis.

Patients with a history of HSV keratitis should be educated about their relative risk of recurrence, acquainted with the signs and symptoms of recurrence, and informed that they should consult an ophthalmologist promptly if they experience warning signs or symptoms. Avoiding or correcting predisposing factors (see disease modifiers) may reduce the risk of HSV keratitis. However, early detection and appropriate treatment are critical to minimize permanent visual loss.

There is one retrospective cohort study comparing systemic and topical acyclovir therapy for the prevention of HSV keratitis recurrences following penetrating keratoplasty.[175] In this study, 26 patients were treated with oral acyclovir at 400 mg twice daily, and 29 patients were treated with 3% topical acyclovir ointment five times daily for an average of 16 months. Patients were followed for an average of 24 months. There was a statistically significant reduction of HSV keratitis recurrence in the patients treated with oral acyclovir when compared to those treated with topical acyclovir at one and two years.[175] It is noteworthy that recurrences of HSV keratitis in the oral acyclovir group in this study occurred only in the first postoperative year. Therefore, either oral antiviral prophylaxis for one year has a protective effect even in the following year, or most HSV keratitis recurrences happen in the first postoperative year.

While most clinical trials of oral antiviral prophylaxis in the setting of penetrating keratoplasty used acyclovir, existing evidence suggests other available oral antiviral agents with activity against HSV can be used. There is one retrospective review comparing valacyclovir (500 mg two to three times daily for four months and tapered to 250 mg twice daily for up to 30 months) to acyclovir (800 mg three to five doses per day and tapered to 400 mg twice daily for 11 to 36 months) prophylaxis following penetrating keratoplasty.[176] This study concluded that there was no difference in recurrence rates, graft failure, or side effects in the two groups.

One interventional case series of 13 patients with a history of recurrent HSV keratitis investigated the efficacy of oral acyclovir prophylaxis at different doses.[177] This study concluded that recurrences were more likely in patients on relatively lower doses (less than 800 mg per day) and in those who had undergone ocular surgery within the previous six weeks. Among the patients experiencing recurrent HSV keratitis following ocular surgery, those on higher doses of oral acyclovir (an average dose of 1321 mg/day) experienced fewer recurrences compared to those on lower doses (average of 1000 mg/day).

Oral acyclovir in doses of 800 mg/three times a day, initially, and later tapered to 400 mg/twice a day for at least one year, dramatically reduces the recurrence rate of HSV keratitis in patients after penetrating keratoplasty. It is reasonable to continue prophylaxis as long as the patient remains on a topical corticosteroid. *(Strong Recommendation, Good Quality)*

HERPES SIMPLEX VIRUS VACCINES

There are no FDA approved vaccines for the prevention of herpes simplex infection or recurrence. There have been relatively few clinical trials investigating the efficacy of a vaccine in the prevention of ocular HSV infections. However, numerous research studies have been focused on the efficacy of vaccines in the prevention of genital herpes infections.

One published study investigated the use of an HSV-1 vaccine to prevent recurrent herpetic ocular disease in humans. This randomized, non-placebo controlled trial enrolled 20 patients with a recent (< 1 year) history of recurrent herpetic ocular disease.[178] Ten patients received repeated injections of heat-inactivated HSV-1, while a comparable control group of the same size did not receive the vaccine. The follow-up period lasted 12 months and commenced on the day the first dose of vaccine was administered in the treatment group and on the last examination of the pre-inclusion period for controls. This study concluded that both the number and duration of ocular HSV-1 recurrences of any type were significantly reduced in those study subjects who received the vaccine. Patients in the vaccine group had 4.0 +- 3.53 recurrences pre-inclusion compared to 1.5 +- 1.27 (p=0.016) recurrences post-inclusion. The duration of recurrences was 21.1 +- 11.5 days pre-treatment compared to 12.3 +- 10.3 days post vaccination (p=0.05). There was no significant difference comparing the pre- and post-inclusion periods in the control group; 2.1 +- 1.37 relapses pre-inclusion and 2.3 +- 1.7 post-inclusion, with a duration of 19.1 +- 7.3 days pre-inclusion and 20.9 +- 11.9 days post-inclusion. The study did not detect any significant change in T-cell subsets of either group.

There are no clinical trials looking specifically at the role of vaccines in prevention of primary ocular herpes simplex infection. There are promising data on the efficacy of a herpes simplex vaccine in the prevention of genital herpes. A randomized double-blind, placebo-controlled Phase III trial investigated the safety and efficacy of a HSV-2 glycoprotein D vaccine in preventing genital or non-genital herpes caused by HSV-1 or HSV-2.[179] This study enrolled 8,323 women 18–30 years of age who were seronegative for HSV-1 and HSV-2 prior to the study. Over the course of 20 months, serial serum specimens were obtained, and exams were performed when genital or non-genital herpes was suspected at any time. While the HSV vaccine was not effective in preventing HSV-2 infections, it was effective in preventing HSV-1 infections. The attack rate of genital herpes caused by HSV-1 was 0.3% in the vaccine group compared to 0.7% in the control group, resulting in a vaccine efficacy of 58%. The attack rate of genital herpes caused by HSV-2 was 0.6% in the vaccine group compared to 0.5% in the control group, resulting in a vaccine efficacy of –38%. There are nine other clinical trials investigating this particular vaccine listed on www.clinicaltrials.gov. These studies have all been completed, but results are pending.

CARE PROCESS

PATIENT OUTCOME CRITERIA

Outcome criteria for treating HSV keratitis include the following:

- Resolution of corneal infection/inflammation
- Reduction in pain
- Minimization of corneal scar and neovascularization
- Prevention of corneal perforation
- Restoration/preservation of visual function

DIAGNOSIS

Evaluation of the patient with presumed HSV keratitis includes those features of the comprehensive medical eye evaluation specifically relevant to the disorder as listed below.

History

Obtaining a detailed history is important in differentiating patients with HSV keratitis from other conditions affecting the cornea. Pertinent information includes the following:

- Ocular symptoms: degree of pain, redness, discharge, blurred vision, photophobia, duration of symptoms, circumstances surrounding the onset of symptoms
- Contact lens history: wearing schedule, overnight wear, type of contact lens, contact lens solution, contact lens hygiene protocol, tap-water rinse of contact lenses, swimming, using a hot tub or showering while wearing contact lenses
- Review of other ocular history, including risk factors such as previous HSV keratitis
- Review of other medical problems and systemic medications
- Current and recently used ocular medications
- Medication allergies

Examination

The physical examination includes measurement of visual acuity, external examination, and slit-lamp biomicroscopy.

Visual Acuity

Patient discomfort, photophobia, and tearing may compromise determination of visual acuity. It is important, however, to document baseline visual acuity and to ascertain that it is consistent with the anterior segment examination.

External Examination

An external examination should be performed with particular attention to the following:

- General appearance of the patient, including skin conditions
- Facial examination
- Preauricular adenopathy
- Globe position
- Eyelids and eyelid closure
- Conjunctival discharge
- Nasolacrimal discharge

- Corneal sensation

Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy should include evaluation of the following:

- Eyelid margins
    - Inflammation
    - Ulceration
    - Eyelash abnormalities, including trichiasis/distichiasis
    - Lacrimal punctal anomalies
    - Ectropion/entropion
- Conjunctiva
    - Discharge
    - Inflammation
    - Morphology (e.g., follicles, papillae, cicatrix, keratin, membrane, ulceration, and scarring)
    - Epithelium, including focal and geographic defects
    - Ischemia
    - Foreign body
    - Filtering bleb
- Sclera
    - Inflammation
    - Ulceration
    - Scar/thinning
    - Nodule
    - Ischemia
- Cornea
    - Epithelium, including defects and their pattern (punctate, dendritic, geographic), edema
    - Stroma, including scar, ulceration, thinning, perforation, and infiltrate (location [central, peripheral, perineural, surgical, or traumatic wound], density, size, shape [ring], number [satellite], depth, character of infiltrate margin [suppurative, necrotic, feathery, soft, crystalline], color), edema
    - Endothelium, including presence of keratic precipitates, guttae
    - Foreign body, including sutures
    - Signs of corneal dystrophy (bilaterality)
    - Previous corneal inflammation (thinning, scarring, or neovascularization)
    - Signs of previous corneal or refractive surgery
- Fluorescein or Rose Bengal staining of the cornea to reveal or confirm the presence of dendrites, pseudodendrites, loose or exposed sutures, foreign body, and any epithelial defect and its morphology
- Iris for transillumination defects
- Anterior chamber for depth and the presence of inflammation, including cell and flare, hypopyon, fibrin, hyphema
- Anterior vitreous for the presence of inflammation
- Contralateral eye for clues to etiology as well as possible similar pathology

Diagnostic Tests

In cases of typical HSV epithelial keratitis (dendritic), clinical diagnosis by slit-lamp biomicroscopy examination is reliable and laboratory tests are usually not needed. Laboratory testing is also not useful in HSV stromal keratitis because a virus usually cannot be cultured. In atypical cases of HSV keratitis, however, laboratory tests may be indicated. The attributes and limitations of the most commonly used diagnostic tests are discussed in this section.

Culture

Isolation of HSV-1 by cell culture is considered the gold standard in laboratory diagnosis of HSV epithelial keratitis.[180] While this technique provides excellent specificity, its use in clinical practice is limited by its low sensitivity[181-183] as well as the length of time required to obtain a result (up to ten days after incubation).[184] Samples must be obtained within several days of the onset of symptoms. Culture swabs are either placed in viral or *Chlamydia* transport media and must be maintained at 4°C until plated on cell culture. When considering culture for HSV keratitis, it is important to avoid use of Rose Bengal dye for corneal staining since it is virucidal when exposed to light. Cultures obtained after corneal staining with Rose Bengal may be falsely negative.[185]

The speed of HSV isolation in culture is improved with use of shell vial culture assays with similar sensitivity and specificity to traditional culture.[180, 186, 187] The presence of HSV can be detected in 70–80% of otherwise culture positive cases.[188] The yield may be lower when antiviral therapy has been used.

Pros: high specificity
Cons: low sensitivity, technically challenging, requires a skilled virology laboratory, relatively slow

Direct Fluorescent Antibody (DFA)

Direct fluorescent antibody (DFA) detection of HSV antigen offers rapid and relatively reliable results. A corneal swab smeared on a slide may be used to obtain a result within minutes. In one investigation, the sensitivity and specificity of DFA detecting HSV antigen in patients with HSV keratitis was determined as 87.5% and 85.3%, respectively.[189] Although the sensitivity of DFA appears to be less than polymerase chain reaction (PCR) and culture,[189, 190] it has a higher specificity when compared to PCR.[189] Direct fluorescent antibody detection may be useful in a setting where PCR is unavailable and a diagnosis needs to be made more rapidly than culture allows. Direct fluorescent antibody requires an ultraviolet microscope and is therefore not always available. It should be noted that use of topical fluorescein prior to acquiring the sample interferes with the DFA test.

Pros: high sensitivity and specificity, rapid
Cons: requires skilled technician, expensive equipment, not widely available

Polymerase Chain Reaction (PCR)

Polymerase chain reaction detection of viral DNA has proven to be as specific, and more sensitive, than cell culture in the diagnosis of HSV epithelial keratitis.[189-193] In one investigation, the sensitivity and specificity of PCR detecting HSV DNA in patients with HSV keratitis was determined as 100% and 67.9%, respectively.[189] In patients with HSV epithelial keratitis, HSV

can be detected from both the tear film and cornea of infected patients.[194, 195] The use of PCR is limited by the need for a skilled technician and special instrumentation and a facility that has established appropriate parameters for ocular specimens. The interpretation of PCR is further limited by its potentially high sensitivity and inability to differentiate pathologic levels of HSV from normal HSV shedding in the tear film.[34, 196, 197] Real-time PCR provides quantification of viral copy numbers, which may allow differentiation of viral shedding from replication. The sensitivity and specificity for detecting HSV-1 by quantitative PCR was reported at 91% and 100%, respectively.[193]

Pros: highest level of sensitivity, rapid
Cons: unable to discriminate shedding from infection, requires skilled technician, expensive equipment, not widely available

Less Useful Diagnostic Tools

Tzanck Smear

Scrapings from the corneal epithelium, or ulcerated eyelid margin or conjunctiva can be obtained with a sterile platinum spatula, smeared on a slide, stained using the Papanicolaou or Giemsa method, and examined by light microscopy. Positive smears show multinucleated giant cells and intranuclear eosinophilic inclusion bodies (Cowdry type A). One study evaluated three different diagnostic tests against the gold standard of viral isolation in 170 patients diagnosed with keratitis of possible HSV etiology. A total of 170 corneal scrapings were obtained and HSV-1 was isolated in 14 cultures.[189] The sensitivity and specificity of detecting HSV with the Giemsa staining method in patients with suspected HSV keratitis was determined as 57.1% and 85.9%, respectively.[189] In spite of its low sensitivity, smears provide a rapid and cheap test readily available in most hospital laboratories.

Pros: high specificity, ease of use, low cost, rapid, widely available
Cons: low sensitivity

Cytology

Cytology can be suggestive of HSV epithelial keratitis and can be performed quickly, but the specificity is too low to provide a diagnosis whether by brush or impression. The sensitivity of cytology is also quite low and a negative result does not rule out an HSV infection.[186, 198]

Pros: ease, cost, rapid, widely available
Cons: low sensitivity and specificity

Enzyme Linked Immunosorbent Assay (ELISA)

Similar to DFA, ELISA uses monoclonal antibodies against HSV specific antigens. Enzyme linked immunosorbent assay has relatively low sensitivity and high specificity. One study concluded that a commercial test, Herpchek™, did not provide any greater sensitivity than a clinical exam.[199] In spite of the low sensitivity, ELISA may be useful when there is a diagnostic dilemma and the clinician requires a more prompt diagnosis than culture isolation can provide. Enzyme linked immunosorbent assay test kits do not require special equipment or expertise and a result is typically available within one hour.

Pros: high specificity, ease, cost, quick, widely available
Cons: low sensitivity

Serology
Since HSV keratitis most commonly represents a reactivation of latent HSV infection, serology has a limited role in diagnosis in most cases. Independent of clinical recurrences, HSV-specific serum IgG antibody levels may fluctuate, and therefore, IgG titer may have limited utility unless negative, and even then, negative serology does not absolutely rule out HSV infection. Immunoglobulin M (IgM) antibodies to HSV are found in primary HSV infection; seroconversion with IgG typically occurs 2–4 weeks after infection. Therefore, serology may be useful in children and young adults where either testing may show HSV-specific IgM; indicating a primary infection, or no antibodies, in which case HSV would be less likely. Serology may also be useful in patients with atypical disease. When ordering HSV serology, it is important to request both IgG and IgM for HSV-1 and HSV-2. Serial titers tested one month apart can be informative.

Pros: ease, widely available
Cons: low specificity, low utility

Other Diagnostic Tools for Special Circumstances
Antiviral Susceptibility Testing
Acyclovir resistance amongst immunocompetent patients with HSV keratitis can be as high as 6.4%.[200, 201] Resistance to acyclovir may occur more commonly in patients with recurrent ocular HSV infections.[200] Compared to patients with HSV keratitis caused by an HSV isolate sensitive to acyclovir, patients infected by an acyclovir-resistant isolate have a higher rate of blindness.[200, 202] Mutations in thymidine kinase (TK) account for the majority of cases with acyclovir resistance.[201, 202] Patients with acyclovir resistant strains of HSV caused by a TK mutation are also resistant to valacyclovir, ganciclovir, and famciclovir because these antiviral agents also rely on TK phosphorylation. Antiviral agents that do not rely on TK phosphorylation (foscarnet, cidofovir, and trifluridine) will not share cross-resistance to acyclovir when there is a TK mutation. Patients with a TK mutation causing acyclovir resistance can be treated with systemic foscarnet.[200, 201] An HSV resistant to both foscarnet and acyclovir can be effectively treated with cidofovir.[203-208] The role of topical trifluridine in the treatment of acyclovir-resistant, mucocutaneous HSV seemed promising in a pilot study conducted in 1996, but no further studies have been conducted.[209] Trifluridine would be expected to be effective in patients with HSV epithelial keratitis with a known TK mutation since it is triphosphorylated intracellularly to its active form by cellular enzymes independent of an HSV-specific thymidine kinase.[210]

Specific antiviral susceptibility testing may be indicated in patients with a history of frequently recurrent ocular HSV despite oral prophylaxis, or in immunocompromised patients, when systemic therapy fails. *(Strong Recommendation, Moderate Quality)*

Susceptibility testing may be performed with direct sequencing of clinical specimens or after amplification of viral isolates.[200-202] In rare cases (less than 5%), acyclovir-resistance may occur due to a mutation in the DNA polymerase gene.[201] Unlike the patients with a TK mutation,

patients with a DNA polymerase gene mutation may be resistant to acyclovir, valacyclovir, ganciclovir, famciclovir, and foscarnet.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of HSV epithelial keratitis includes other infectious keratitis, in particular *Acanthamoeba* keratitis, varicella zoster virus epithelial keratitis, Epstein-Barr virus epithelial keratitis, adenovirus epithelial keratitis, *Chlamydia* epithelial keratitis, and other bacterial epithelial keratitis when the stroma is not yet involved. Noninfectious causes of dendritiform and/or geographic epithelial ulcerations include epithelial regeneration lines after abrasion, or in neurotrophic keratopathy, recurrent epithelial erosion, persistent epithelial defect, exposure keratopathy, Thygeson's superficial punctuate keratitis, limbal stem cell failure, cornea verticillata from amiodarone deposition and Fabry's disease, tyrosinemia, and epithelial lesions from topical beta-blockers. Neurotrophic keratopathy and persistent epithelial defect can also be consequences of recurrent and/or severe HSV keratitis.

The differential diagnosis of HSV stromal keratitis without ulceration includes any cause of interstitial keratitis, including syphilis, Cogan's syndrome, varicella zoster virus keratitis, Epstein-Barr virus keratitis, measles keratitis, mumps keratitis, Lyme disease, and others.

The differential diagnosis of HSV stromal keratitis with ulceration includes all forms of microbial keratitis, including from infection by bacteria, fungi, and *Acanthamoeba*, varicella zoster keratitis, sterile keratolysis from chemical injuries and autoimmune diseases, exposure keratopathy, and neurotrophic keratopathy.

The differential diagnosis of HSV endothelial keratitis includes any form of keratouveitis, Posner Schlossman syndrome, CMV endothelial keratitis, and corneal graft rejection.

TREATMENT

Treatment Recommendations: HSV Epithelial Keratitis

Antiviral agents alone are the treatment of choice for HSV epithelial keratitis. Topical corticosteroids should be avoided in the initial management of HSV epithelial keratitis. See Appendix VI for treatment options and dosing. *(Strong Recommendation, Good Quality)*

Antiviral agents are the preferred method of treatment for HSV epithelial keratitis. There are 11 antiviral agents with proven efficacy against HSV (Appendix I). Three are no longer manufactured (idoxuridine, vidarabine, and brivudine), and the use of three others (valganciclovir, foscarnet, and cidofovir) is limited by a poor safety profile. There are two topical (trifluridine and ganciclovir) and three systemic (acyclovir, famciclovir, and valacyclovir) antiviral agents available and actively used for the treatment of HSV epithelial keratitis in the United States (See Support Document I and II). Trifluridine solution and topical ganciclovir gel are the only two antiviral agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of HSV. While oral antivirals are widely used in HSV keratitis, their use is considered off label. The following treatment recommendations address the antiviral agents available in the U.S., with the addition of topical acyclovir, which is not FDA approved as a

topical ophthalmic agent, but is widely used outside the U.S. There are no studies comparing the two FDA-approved topical antiviral agents (ganciclovir and trifluridine) or between topical trifluridine or topical ganciclovir and systemic acyclovir, valacyclovir, or famciclovir. All published comparative efficacy trials to date involved topical acyclovir. Thus, topical acyclovir has been used as a proxy below for comparing various antiviral agents.

Adequate corneal tissue levels (demonstrated by aqueous humor concentrations greater than the median effective dose (ED50) have been reported with both topical trifluridine solution and acyclovir ointment,[211-214] as well as systemic acyclovir and valacyclovir.[215, 216] Whereas oral acyclovir in a dosage of 400 mg five times daily provides therapeutic levels in the aqueous humor,[217] adequate aqueous humor concentrations of trifluridine can only be achieved when the cornea has an epithelial defect. Trifluridine penetration doubles in patients after corneal epithelial debridement, or in the presence of a corneal epithelial defect, when compared to patients with an intact corneal epithelium.[212, 213, 218] In contrast, topical acyclovir achieves therapeutic levels which exceed the (ED50) in the aqueous humor of humans with an intact corneal epithelium.[218] It is unclear, based on the published literature, if topical ganciclovir gel 0.15% penetrates the corneal stroma at a concentration sufficient to exceed the ED50.[214] The single published study showed ganciclovir failed to meet the ED50 in aqueous humor with the currently marketed concentration (0.15%) in ganciclovir gel. Adequate aqueous humor levels were demonstrated with a higher concentration (0.2%) in rabbits with dendritic ulcers, but with high variability, and nominal aqueous humor levels were observed when using lower concentrations (0.05% and 0.0125%).[219] Ganciclovir ointment 3% achieved adequate aqueous humor concentration levels in normal corneas of rabbits, but this dose is 20 times the currently marketed (0.15%) formulation.[219] (See Appendix II and Support Document III.) The aqueous and vitreous humor concentrations for oral famciclovir exceed the ED50 for HSV.[174, 220] (See Appendix II and Support Document III.)

1. Treatment Options

a. Topical Antiviral Agent

Both topical trifluridine solution and ganciclovir gel are safe and effective and have been FDA approved for the treatment of HSV epithelial keratitis. While there are no clinical trials directly comparing topical ganciclovir gel to trifluridine solution, several clinical trials were performed comparing one or the other to topical acyclovir ointment. Three double blind randomized clinical trials comparing trifluridine ointment to acyclovir ointment concluded that the efficacy of these two antiviral agents are similar, and that both agents are highly effective in the treatment of HSV epithelial keratitis.[221-223] Similarly, three unmasked randomized clinical trials concluded that the efficacy of ganciclovir gel and acyclovir ointment in the treatment of HSV epithelial keratitis do not significantly differ.[224-226] Thus considering acyclovir ointment as a proxy, topical ganciclovir and trifluridine can be considered roughly equal in efficacy in the treatment of HSV epithelial keratitis. While both topical antiviral agents appear to be effective treatment options, there may be advantages to choosing one topical agent over the other in select cases. (See Appendix III and Support Document I.)

b. Oral Antiviral Agents

Oral antiviral agents appear to be safe and effective for the treatment of HSV epithelial keratitis, but are not specifically FDA approved for the condition. Three oral antiviral agents (acyclovir, valacyclovir, and famciclovir) demonstrate acceptable safety and proven effectiveness for HSV

infections. The efficacy of oral antiviral agents for the treatment of HSV epithelial keratitis, when compared to topical acyclovir ointment, was demonstrated in two double blind placebo controlled randomized clinical trials. Both studies compared acyclovir 400 mg five times daily to topical acyclovir ointment five times daily, and concluded that oral acyclovir performed at least as well as topical acyclovir in the treatment of HSV epithelial keratitis.[227, 228] There are no clinical trials demonstrating the efficacy of valacyclovir or famciclovir for the treatment of HSV epithelial keratitis, but there are several studies demonstrating their efficacy in the prevention of herpes simplex keratitis recurrence.[173, 174] Oral antiviral agents should be used with caution in elderly patients ($\geq$ 65 years old) and those with renal impairment, as all three oral antiviral agents have the potential to cause nephrotoxicity.

All three oral antivirals are designated Pregnancy Category B.[2a] However, a large population-based, historical cohort study of 837,795 live-born infants in Denmark found no association between first trimester exposure to valacyclovir or acyclovir and major birth defects.[229] Famciclovir was also included in this study, but exposure to the drug was uncommon and the evidence insufficient to support its safety during pregnancy. In spite of their similar safety and efficacy profiles, there may be advantages to choosing one oral antiviral agent over the other in select cases. (See Appendix IV and Support Document II.)

c. Debridement

Although the clinical use of debridement in HSV epithelial keratitis is long standing, the published literature offers strong evidence that debridement alone is inadequate treatment for HSV epithelial keratitis. One randomized, non-placebo controlled clinical trial compared the following three treatment arms; minimal wiping debridement alone, minimal wiping debridement plus topical trifluridine, and topical trifluridine alone.[230] The study concluded that debridement alone was statistically less effective in the number of HSV ulcers healed, than either an antiviral alone or with the combination of antiviral and debridement. An additional randomized, double blind, placebo controlled clinical trial compared minimal wiping debridement and placebo to minimal wiping debridement plus topical acyclovir in the treatment of HSV epithelial keratitis.[231] This clinical trial recorded the number of recurrences of typical HSV epithelial keratitis in the seven days following treatment. Typical epithelial lesions were defined as either punctate foci of opaque swollen epithelial cells that enlarge over 1–2 days or typical epithelial dendritic ulcers. All of the recurrences in the seven days following debridement occurred in the placebo group and none in the topical acyclovir group. In a separate randomized double blind placebo controlled trial, the addition of oral acyclovir to minimal debridement improved healing time.[232] Another randomized, non-placebo controlled clinical trial concluded that minimal wiping debridement, when added to topical acyclovir ointment offered no improvement in either the number of ulcers healed or the rate of healing.[233] However, in two separate randomized (non-placebo controlled) clinical trials, patients treated with a combination of topical trifluridine solution and blunt spatula debridement[234] or a combination of acyclovir ointment plus gentle wiping debridement[235] healed faster than those treated with the topical antiviral agent alone. In summary, the evidence to support the addition of debridement to use of an antiviral agent is weak and lacks coherence.

[2a] Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

d. Interferon

While topical preparations of interferon α2B exhibit antiviral activity against HSV epithelial keratitis, the clinical use of topical interferon remains experimental, is limited by the availability of sufficiently concentrated interferon in the U.S. market, and is not FDA approved. (See Support Document V.)

Summary of Treatment Recommendations: HSV Epithelial Keratitis

There are two FDA approved topical antiviral agents with similar efficacy (ganciclovir and trifluridine). There are three oral antiviral agents (acyclovir, valacyclovir, and famciclovir) available in the U.S. Oral antiviral agents appear to be as effective as topical antiviral agents (ganciclovir, trifluridine) in the treatment of HSV epithelial keratitis. In spite of their similar efficacy, there are differences and there may be advantages to choosing one over the other in individual cases (see Appendix V). There is no evidence that simultaneous use of two antiviral agents, whether topical or oral, accelerates healing of HSV epithelial keratitis (see Support Document IV). Debridement alone is not recommended for the treatment of HSV epithelial keratitis. When antiviral agents are contraindicated or unavailable, debridement may be used as an alternative treatment. The addition of minimal wiping debridement to a topical antiviral agent may be of limited or no benefit. Topical acyclovir ointment is effective against HSV epithelial keratitis, but is unavailable in the U.S.

Treatment Recommendations: HSV Stromal Keratitis

A topical corticosteroid agent in conjunction with an oral antiviral agent for at least ten weeks is the preferred treatment for HSV stromal keratitis. The balance between antiviral and corticosteroid therapy should be adjusted depending on the presence or absence of epithelial ulceration. See Appendix VI for treatment options and dosing. *(Strong Recommendation, Good Quality)*

The results of a double blind, placebo controlled randomized clinical trial by the HEDS group clearly supports the use of a topical corticosteroid in the treatment of HSV stromal keratitis.[236] Patients in this study were treated with a ten-week taper of topical prednisolone plus trifluridine solution or topical placebo with trifluridine. During the ten-week course of trial medications, 26% of the patients in the corticosteroid group failed treatment compared to 73% of the patients in the placebo group. The authors concluded that patients treated with a ten-week taper of topical prednisolone plus trifluridine solution experienced more rapid resolution than when treated with trifluridine solution alone.[236] Further, patients treated with a combination of topical prednisolone and trifluridine solution were less likely to fail treatment. While a distinct difference was appreciated between the two treatment groups during the treatment period, the study also demonstrated that ten weeks of tapered corticosteroids may be too brief: one half of the patients treated with the combination of a topical antiviral and topical corticosteroid and 76% of the patients in the placebo group failed within six weeks of corticosteroid cessation. In a second HEDS study, 75% of the patients receiving a ten-week taper of topical prednisolone, topical trifluridine, and oral acyclovir, and 74% of the patients' receiving the same regimen except for placebo instead of oral acyclovir had failed treatment six weeks after treatment ended.[237] Therefore, a tapered course of topical corticosteroids for greater than ten weeks is recommended.
For HSV stromal keratitis, oral antiviral agents are preferred to the two topical antiviral agents

available in the United States (trifluridine solution and ganciclovir ophthalmic gel). The long term use of topical trifluridine solution causes toxic keratoconjunctivitis, allergic conjunctivitis, and punctal stenosis.[7, 18, 238] Long-term use of topical ganciclovir ophthalmic gel has not been studied and neither topical trifluridine or ganciclovir show adequate penetration of the corneal stroma.[214, 218, 219] (See Appendix II and Support Document III). Therefore, oral antiviral agents — in conjunction with a topical corticosteroid — are preferred for the treatment of HSV stromal keratitis.

The HEDS group demonstrated no additional benefit to adding an oral antiviral agent to a treatment regimen, which already includes a topical antiviral agent.[237] Patients in this double blind, placebo controlled randomized clinical trial were treated with a ten- week course of topical prednisolone and trifluridine solution, plus either oral acyclovir 400 mg or placebo five times daily for ten weeks. The patients treated with oral acyclovir (in addition to topical corticosteroid and topical trifluridine solution) failed treatment in 85 days, while the patients treated with placebo failed treatment in 62 days. Further, the treatment failure rates before completing the ten-week course of trial medication were 38% in the acyclovir group and 48% in the placebo group. However, the addition of oral acyclovir to topical corticosteroid and trifluridine failed to demonstrate a statistically significant difference in median time to treatment failure.[237] No study to date has demonstrated any statistical benefit to using two currently available antiviral agents over a single antiviral agent, whether oral or topical.[237, 239, 240]

A role for topical cyclosporine in patients with HSV stromal keratitis without ulceration was suggested by two case series using 2% cyclosporine in oil [241, 242] and one case series with 0.05% cyclosporine in an emulsion (Restasis®).[243] These three reports suggest that cyclosporine might be useful as adjunctive therapy to replace or reduce the need for topical corticosteroids in patients with concurrent HSV stromal keratitis without ulceration and steroid-induced glaucoma. A randomized, placebo controlled clinical trial demonstrated that patients treated with topical cyclosporine emulsion in concentrations ranging from 0.05% to 0.4% do not experience an increase of intraocular pressure,[244] suggesting topical cyclosporine may be useful as a steroid minimizing adjunct in the treatment of HSV stromal keratitis.

Herpes simplex virus stromal keratitis with epithelial ulceration presents less commonly than HSV stromal keratitis without ulceration, and is the form of HSV keratitis most often confused with microbial keratitis. There are very few studies focusing specifically on HSV stromal keratitis with epithelial ulceration. Most of the patients in the two HEDS trials above[236, 237] had HSV stromal keratitis without epithelial ulceration — only 9% and 12% of patients, respectively, had stromal keratitis with ulceration. The numbers of patients with HSV stromal keratitis with epithelial ulceration in the HEDS trials were too small to determine the best course of therapy. One case series of 15 patients reported success combining amniotic membrane graft with topical corticosteroid and antiviral treatment for the treatment of HSV stromal keratitis with ulceration,[245] but a role for amniotic membrane transplantation in HSV keratitis remains speculative. Electron microscopic examination of pathologic tissue from patients with HSV keratitis with epithelial ulceration detected intact virions in stromal keratocytes,[246] suggesting a possible need to obtain therapeutic levels with oral antiviral therapy when the epithelium is ulcerated in HSV stromal keratitis.

Summary of Treatment Recommendations: HSV Stromal Keratitis

In summary, the recommended treatment for HSV stromal keratitis without ulceration should include a topical corticosteroid for at least ten weeks in conjunction with a prophylactic oral antiviral. A treatment period greater than ten weeks has been recommended since both double blind, placebo controlled randomized clinical trials by the HEDS group found excessively high treatment failure rates six weeks after a ten-week prednisolone taper (50%[236] and 75%[237]), indicating the length of treatment may have been inadequate. The treatment course should be titrated empirically depending on the clinical response. Oral antiviral agents are recommended over topical antiviral agents for their safety profile and superior corneal penetration. The best treatment for HSV keratitis with epithelial ulceration has not been studied adequately in randomized clinical trials, but available evidence suggests a role for therapeutic doses of oral antiviral combined with judicious use of topical corticosteroids.

Treatment Recommendations: HSV Endothelial Keratitis

A topical corticosteroid agent in conjunction with an oral antiviral agent is the preferred treatment for HSV endothelial keratitis. See Appendix VI for treatment options and dosing. *(Strong Recommendation, Good Quality)*

Herpes simplex virus endothelial keratitis is relatively uncommon and usually presents independently of other forms of HSV keratitis. Historically, HSV endothelial keratitis has often been referred to as disciform keratitis because some patients present with a discrete, well demarcated round or oval area of keratic precipitates with overlying corneal edema. However, endothelial keratitis may also involve the entire cornea in which case "disciform" is inaccurate and does not fully describe the disorder.

Only a few studies exist to guide treatment recommendations for HSV endothelial keratitis.[247-251] These compare the combination of topical acyclovir 3% ointment and topical betamethasone (at 0.1%[249, 251] or 0.01%[248]) with acyclovir ointment alone.[227, 248, 249, 251] In all studies, treatments were administered five times daily. These randomized double blind trials concluded that in cases of HSV endothelial keratitis, a topical corticosteroid agent in conjunction with a topical antiviral agent produced a faster response,[248, 249, 251] and with significantly fewer treatment failures,[248, 251] than a topical antiviral agent alone.

An additional open label study of 43 patients with HSV endothelial keratitis compared topical acyclovir ointment 3% five times daily to oral acyclovir 400 mg five times daily in patients also treated with topical prednisolone 0.05%.[250] There was no difference in mean time to healing between the oral (25.9 days) and topical (25.3 days) treatment groups. However, the oral acyclovir group demonstrated significantly faster resolution of lacrimation and greater improvement of visual acuity.

The mean healing time for the patients requiring treatment with combination antiviral and corticosteroid therapy ranged from 21 days[248, 249, 251] to 25 days[250] in these studies. Compared to patients with HSV stromal keratitis, those with HSV endothelial keratitis appear to respond more rapidly to treatment and may not require prolonged therapy.

Unlike topical acyclovir, the two topical antiviral agents available in the U.S., trifluridine and ganciclovir, do not achieve adequate corneal penetration (see Appendix II and Support Document III) and are not recommended for the treatment of HSV endothelial keratitis. An oral antiviral agent is recommended to ensure adequate corneal penetration[217] in the treatment of HSV endothelial keratitis.[250]

Summary of Treatment Recommendations: HSV Endothelial Keratitis
In summary, the recommended treatment for HSV endothelial keratitis includes a topical corticosteroid in conjunction with an oral antiviral agent.

THERAPY FOR COMPLICATED CASES (See Appendices III, IV, V, and IV)
Children and atopic individuals with HSV keratitis may prove relatively difficult to manage and may require relatively higher doses of oral antivirals. The occurrence of HSV epithelial keratitis simultaneous to stromal or endothelial keratitis is uncommon and may occasionally require concurrent use of both antiviral and corticosteroid therapy, but in general it is advisable to avoid or minimize topical corticosteroid use in the setting of HSV epithelial keratitis. In general, patients with renal insufficiency require reduced doses of oral antivirals and longer intervals between administrations. Dosing of oral antivirals in patients with renal insufficiency should be coordinated with a nephrologist. (See Appendix VI.)

PROVIDER AND SETTING
The diagnosis and management of patients with HSV keratitis require the clinical training and experience of an ophthalmologist because the disease has the potential to cause visual loss or blindness.

COUNSELING/REFERRAL
Patients and care providers should be educated about the destructive nature of HSV keratitis and the need for strict adherence to the therapeutic regimen. The possibility of permanent visual loss and need for future visual rehabilitation should be discussed. Patients with HSV keratitis should be educated about the risk of recurrence.

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APPENDIX I: Antiviral Agents Effective Against Herpes Simplex Virus

Formulation	Antiviral Agent	Available in the United States	FDA Approved for HSV-1 Infection	FDA Approved for HSV Keratitis	Limitations
Topical					
	Trifluridine Solution	Yes	Yes	Yes	
	Ganciclovir Gel	Yes	Yes	Yes	
	Acyclovir Ointment	No	Widely used in Europe		
	Idoxuridine	No longer manufactured			
	Vidarabine	No longer manufactured			
	Brivudine	No longer manufactured			
Oral					
	Acyclovir	Yes	Yes	No	
	Valacyclovir	Yes	Yes	No	
	Famciclovir	Yes	Yes	No	
	Brivudine	No	No	No	
	Valganciclovir	Yes	No	No	Safety*
Intravenous					
	Acyclovir	Yes	Yes	No	
	Foscarnet	Yes	Yes	No	Safety*
	Cidofovir	Yes	No	No	Safety*
	Ganciclovir	Yes	No	No	Safety*

* Please see manufacturers' prescribing information for details.

APPENDIX II: Corneal Penetration and Median Effective Dose of Antiviral Agents

Median Effective Dose (ED50)

The median effective dose is a statistically derived dose of drug expected to produce a certain effect in 50% of test organisms. Topical and oral antivirals are both capable of achieving adequate corneal tissue levels. These levels are measured indirectly by the aqueous humor concentration. Drugs in the aqueous humor equilibrate with drugs in the surrounding tissue, including the cornea. Below is a list of established ED50 levels in the published literature.

Topical Antiviral Agents: Corneal Tissue Penetration (Aqueous Concentration)

TRIFLURIDINE
ED50: 0.75–1.81 µM[1]
(plaque reduction method)
15–45 µM[1]
(yield reduction method)
or
ED50: 0.2–1.7 µg/ml[2]

Formulation	**Dosage**	**Therapeutic Level (aqueous humor)****	**Model**
1% Solution	1 drop Q 10 minutes in OR for 4 doses	"Unhealthy" epithelium* 6.4–43.9 µM "Healthy" epithelium 6.4–43.9 µM	Human[3]
1% Solution	1 drop Q 30 minutes preoperatively for 5 doses	No epithelial defect Not detected (sensitivity 2µM or 0.5 mg/ml)	Human[4]
1% Solution	1 drop Q 5 minutes for 4 doses	1. No epithelial defect Mean: 6 µg/ml 2. Dendrite Mean: 37 µg/ml	Rabbit[5]

ACYCLOVIR
ED50: 0.1–1.6 µM[6-11]
or
ED50: 120–240 ng/ml[10]

Formulation	**Dosage**	**Therapeutic Level (aqueous humor)****	**Model**
3% Ointment	4 times daily	Dendrite Mean: 308 ng/ml (s.d.: 146)	Rabbit[10]
3% Ointment	Q 4–6 hours for 4–6 doses prior to surgery	Normal cornea 1.7 µg/ml (7.5 µm) Range: (1.5–1.9 mg/ml)	Human[4]

GANCICLOVIR

ED50: 0.2–0.5 μM[7] (plaque reduction method)			
Formulation	**Dosage**	**Therapeutic Level (aqueous humor)****	**Model**
0.2% Gel	4 times daily for 10 days	Dendrite 394 ng/ml (s.d.: 419)	Rabbit[10]
0.05% Gel	4 times daily for 10 days	Dendrite 18 ng/ml (s.d.: .25)	Rabbit[10]
3% Ganciclovir salt in ointment	Q 5 hours for 6 doses	Normal cornea Mean: 4.73 μM (2 hours post administration) to 1.84 μM (3 hours post administration)	Rabbit[12]

***** The term "unhealthy epithelium" is quoted directly from the cited study, in which epithelial "health" was graded from poor to fair.
** Therapeutic levels are listed as in the original cited reports.

Systemic Antiviral Agents: Corneal Tissue Penetration (Aqueous Concentration)

ORAL ACYCLOVIR ED50: 0.1–1.6 μM[6-11]			
Dosage	**Frequency**	**Therapeutic Level (aqueous humor)****	**Model**
400 mg	Q 4–6 hours times 5 doses prior to surgery	3.26 μM (1.10–5.39)	Human[11]
800 mg	Q 4 hours times 6 doses prior to surgery	5.37 μM	Human[13]
ORAL VALACYCLOVIR ED50: 0.1–1.6 μM[6-11]			
Dosage	**Frequency**	**Therapeutic Level (aqueous humor)****	**Model**
100 mg	Q 8 hours times 3 doses prior to surgery	9.63 μM	Human[13]

ORAL FAMCICLOVIR ED50: 0.04–0.06 µg/ml[14]			
Dosage	**Frequency**	**Therapeutic Level (vitreous humor)**	**Model**
500 mg	Q 8 hours times 3 doses prior to surgery	1.21 µg/ml	Human[15]

Acyclovir ED50 References

Reference	**ED50**	**Type of Study**
Inoue 1989[6]	0.07 µg/ml (0.02–0.14)	In vitro (cell culture, plaque inhibition)
Smee 1983[7]	0.3–0.8 µM	In vitro
Smee 1985[8]	0.5–1.0 µM	In vitro
Castela 1994[10]	180 +/- 63 ng/ml (120–240) Mean=0.8 µM	In vitro
Crumpacker 1979[16]	0.15 µM	In vitro
De Clercq 1980[17]	0.18 µM 0.04 µM/ml	In vitro
Smolin and Thofts, The Cornea[18]	0.1–1.6 µM	Range of means from above references
Betz 2002[19]	22 mg/kg	Murine lethal challenge model

Trifluridine ED50 References

Reference	**ED50**	**Model**
Lin 1976[18]	0.2–1.7 µg/ml	In vitro

Ganciclovir ED50 References

Reference	**ED50**	**Model**
Inoue 1989[6]	0.23 µg/ml (0.062–0.50)	In vitro
Smee 1983[7]	0.2–0.5 µM	In vitro
Smee 1985[8]	0.2–0.5 µM	In vitro
Castela 1994[10]	260 +/- 60 µg/ml (200–320) Mean=1.05 µM	In vitro
Trousdale 1984[20]	Mean 0.23 µg/ml Range: (0.06–0.5)	Rabbit (GCV precursor)

Smith 1984[21]	Mean: 0.23 µg/ml Range: (0.06–0.5)	Rabbit (GCV precursor)
Inoue 1989[6]	Mean: 0.23 µg/ml Range: (0.06–0.5)	In vitro
Betz 2002[19]	2.5 mg/kg	Murine lethal challenge model

Valacyclovir ED50 References

Reference	ED50 (mg/kg)	Model
Betz 2002[19]	17 mg/kg	Murine lethal challenge model

Famciclovir ED50 References

Reference	ED50 (mg/kg)	Model
Betz 2002[19]	17 mg/kg	Murine lethal challenge model

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APPENDIX III: Selecting a Topical Antiviral Agent

In select cases, the choice between the two topical antiviral agents approved by the FDA for the treatment of HSV keratitis may be guided by the following:

Preferred Treatment: Ganciclovir
Ulcer that is refractory to trifluridine treatment.
Ulcers that require prolonged topical therapy (trifluridine treatment limited to 21 days).
Patients physically unable to apply drops every two hours while awake.
Children between the ages of 2–6 (trifluridine approved for children age 6 and older).

Preferred Treatment: Trifluridine
Contact lens wear (ganciclovir warning against contact lens use).
Ulcer that is refractory to ganciclovir treatment.
Lower cost.

APPENDIX IV: Selecting an Oral Antiviral Agent

In select cases, the choice among oral antiviral agents may be guided by the following:

Lactose Intolerant Patients

The brand Valtrex® and the generic drug valacyclovir are recommended for the treatment of HSV keratitis in patients with lactose intolerance. Specific preparations of acyclovir are lactose-free along with preparations by some specific manufacturers of generic famciclovir. In order to avoid lactose without concern, the prescriber should request lactose-free preparations.

Lactose-free brand oral antiviral agents:
1. Zovirax® (acyclovir): 400 mg or 800 mg (200 mg contains lactose)
2. Valtrex® (valacyclovir)

Lactose-free generic oral antiviral agents:
1. Valacyclovir: any strength
2. Famciclovir, manufactured by Teva: any strength
*Generic medications are required to include identical active ingredients, but the inactive ingredients vary between manufacturers. The presence of lactose in generic acyclovir varies between manufacturers. However, the available generic version of acyclovir contains lactose. Several manufactures produce generic famciclovir for the United States and only one is lactose-free (Teva). All strengths of Famvir® (famciclovir) contain lactose. Since the manufacturer is not known until the drug is dispensed, generic famciclovir is not recommended for the lactose intolerant.

Pediatric Patients

1. Acyclovir: safety and efficacy established in neonates and above. (Available in a suspension formula.)
2. Valacyclovir: indicated for children greater than age 2.
*The efficacy and safety of famciclovir has not been established in pediatric patients. Famciclovir is indicated only for patients greater than 18 years of age.

Women of Child-Bearing Age

1. Acyclovir[1]
2. Valacyclovir[1]
*All three oral antiviral agents have been designated Pregnancy Category B. There is evidence to suggest that mothers taking acyclovir and valacyclovir in the first trimester of pregnancy are no more likely to have children with major birth defects when compared to the general population. Too few women were taking famciclovir at the time to support the safety of this drug.[1]

Elderly Patients

Famciclovir
*Famciclovir is preferred to acyclovir and its prodrug valacyclovir in elderly patients (defined by the FDA as $\geq$ 65 years of age), with or without reduced renal function. Acyclovir and valacyclovir use in these patients carries an increased risk of central nervous system adverse reactions, including agitation, hallucinations, confusion, and encephalopathy. Acyclovir and

valacyclovir in elderly recipients also carries an increased risk of acute renal failure as compared to patients < 65 years of age.

Immunocompromised Patients (HIV, Transplant)

Famciclovir, Valacyclovir, or Acyclovir

*While the prescribing information for valacyclovir and acyclovir report the risks below, three randomized controlled trials demonstrated the efficacy and safety of these medications in patients infected with HIV.[2]

Prescribing Information Warning: Valacyclovir has an increased risk of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in patients infected with HIV and in transplant (bone marrow and renal) recipients. Acyclovir has an increased risk of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in patients immunocompromised for any reason.

Patients with Impaired Renal Function

All oral antiviral agents should be used with caution in patients with impaired renal function. All oral antiviral agents require dose adjustment in patients with impaired renal function. (See Appendix VI.)

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APPENDIX V: Selecting an Oral or Topical Antiviral Agent

In select cases, the choice between an oral or topical antiviral agent may be guided by the following:

Preferred Treatment: Oral Antiviral

Patient physically unable to use gel or drops (i.e., patients with intention tremor or arthritis).
Contact lens wearers.
Pediatric patients' refractory to topical antiviral.
Patients that require lengthy treatment antiviral agents (greater than 21 days).
Patients with preexisting ocular surface disease who may be more susceptible to ocular surface toxicity.
Prophylactic treatment after ocular surgery.

Preferred Treatment: Topical Antiviral

Patients with renal impairment (all oral antiviral agents are nephrotoxic).
Elderly patients ($\geq$ 65 years old) with renal impairment or when renal function is unknown at the time of drug administration.
Pregnant patients (all oral antivirals are Category B).
Nursing mothers — acyclovir was demonstrated in breast milk of nursing mothers taking valacyclovir as well as acyclovir. (No studies on famciclovir.)

SUPPORT DOCUMENT I: Topical Antiviral Agents

All of the information below was obtained from the prescribing information ("package insert") supplied by the manufacturers.

Two topical antivirals available in the United States (both FDA approved for HSV epithelial keratitis)

Zirgan® (Ganciclovir Ophthalmic Gel 0.15%)

FDA Approval

Indications: Acute HSV keratitis (dendritic ulcers).

Pediatrics: Children age 2 and above.

Pregnancy: Category C.

Nursing Mothers: Caution should be exercised.

Warnings: Avoid Contact Lenses.

Dosage: 1 drop 5 times daily (Q 3 hours while awake) until healed then 1 drop TID for 1 week.

Adverse Reactions: Blurred vision (60%), eye irritation (20%), punctuate keratitis (5%), and conjunctival hyperemia (5%).

Cost per treatment course according to the Veterans Affairs Administration:
open market price as of 5/3/10: $127.48.

Viroptic® (Trifluridine Ophthalmic Solution 1%)

FDA Approval

Indications: Primary keratoconjunctivitis and recurrent epithelial keratitis due to HSV, types I & II.

Pediatrics: Children age 6 and above.

Pregnancy: Category C.

Nursing Mothers: Should not be prescribed to nursing mothers unless the potential benefits outweigh potential risks.

Warnings: Do not exceed maximum dose due to toxicity.

Dosage: 1 drop Q 2 hours while awake (do not exceed 9 drops per day) until healed then 1 drop 5 times a day for 1 week.

Max Dose: Daily (9 drops), total number of days (21 days).

Adverse Reactions: Mild burning or stinging upon instillation (4.6%) and palpebral edema (2.8%). Other symptoms less than 2.8%: punctuate keratitis, epithelial keratopathy, hypersensitivity reaction, stromal edema, irritation, keratitis sicca, hyperemia, and increased intraocular pressure.

(Trifluridine Ophthalmic Solution 1%, generic)

FDA Approval

Indications: Primary keratoconjunctivitis and recurrent epithelial keratitis due to HSV, types I & II.

Pediatrics: Children age 6 and above.

Pregnancy: Category C.

Nursing Mothers: Should not be prescribed to nursing mothers unless the potential benefits outweigh potential risks.
Warnings: Do not exceed maximum dose due to toxicity.
Dosage: 1 drop Q 2 hours while awake (do not exceed 9 drops per day) until healed then 1 drop 5 times a day for 1 week.
Max Dose: Daily (9 drops), total number of days (21 days).
Adverse Reactions: Mild burning or stinging upon instillation (4.6%) and palpebral edema (2.8%). Other symptoms less than 2.8%: punctuate keratitis, epithelial keratopathy, hypersensitivity reaction, stromal edema, irritation, keratitis sicca, hyperemia, and increased intraocular pressure.
Cost per treatment course according to the Veterans Affairs Administration: open market price as of 5/3/10: $39.20.

SUPPORT DOCUMENT II: Oral Antiviral Agents*

	Acyclovir	**Famciclovir**	**Valacyclovir**
Brand	Zovirax®	Famvir®	Valtrex®
Generic Available	Yes	Yes	Yes
Adult Indications	HSV 1. Genital infection 2. Encephalitis 3. Mucocutaneous VZV 1. Shingles 2. Chickenpox Immunocompromised Patients 1. Prevention of HSV reactivation (HIV and HSCT) 2. Prevention of VZV reactivation (HSCT) 3. Treatment of disseminated HSV or VZV (cancer) 4. Treatment of suspected HSV or VZV encephalitis (cancer) 5. Treatment of episodic HSV infection (HIV)	HSV 1. Genital infection 2. Encephalitis 3. Recurrent labialis VZV 1. Shingles 2. Chickenpox Immunocompromised Patients 1. Recurrent mucocutaneous/ genital (HIV) 2. Prevention of HSV reactivation (HIV)	HSV 1. Genital infection 2. Labialis VZV 1. Shingles 2. Chickenpox Immunocompromised Patients 1. Treatment of HSV or VZV (Cancer) 2. CMV prophylaxis (HSCT)
Pediatric Indications	HSV 1. Genital infection 2. Encephalitis 3. Mucocutaneous 4. Neonatal 5. Prevention of reactivation (HIV exposed or positive patients, HSCT) VZV	none	HSV 1. Labialis VZV 1. Chickenpox

	1. Shingles 2. Chickenpox 3. Acute retinal necrosis (HIV exposed or positive patients)		
Pediatric Age	> 2 years old (neonatal indication)	> 18 years old	> 2 years old
U.S. Dosage Forms	<u>Oral</u> Capsule Tablet Suspension <u>IV</u> Powder Solution	<u>Oral</u> Tablet	<u>Oral</u> Caplets (suspension can be prepared from 500mg caplets)
Disease Related Concerns	1. Renal impairment	1. Renal impairment	1. Renal impairment
Dosage Concerns		1. Lactose intolerance	
Warnings	1. Acute renal failure 2. TTP	1. Acute renal failure	1. TTP/HUS 2. Acute renal failure 3. CNS (agitation, hallucination, encephalopathy)
Pregnancy Category	B	B	B
Dosing Frequency (Chronic Suppressive HSV Therapy)	BID	BID	QD
Adult Half Life	3 hours	2–4 hours	2.5–3 hours

*Based on FDA Prescribing Information.

HSCT: Hematopoetic stem cell transplantation
TTP: ***Thrombotic thrombocytopenic purpura***
HUS: Hemolytic uremic syndrome

SUPPORT DOCUMENT III: Antiviral Penetration of Topical Antiviral Agents

Topical antiviral agents vary in their ability to penetrate the cornea and achieve adequate aqueous humor concentration. Adequate aqueous concentrations of trifluridine, for example, can only be achieved when the cornea has been debrided or damaged. The corneal penetration of trifluridine doubles in patients with debrided or damaged corneal epithelium when compared to patients with an intact corneal epithelium (Pavan-Langston 1979, Sugar 1973, Poirier 1982). However, topical acyclovir has been proven to achieve adequate aqueous humor concentrations in humans with an intact corneal epithelium (Poirier 1982). Topical ganciclovir, at doses 20 times the currently marketed strength, achieved adequate aqueous humor concentration levels in rabbits with normal corneas (Schulman 1986). There are no studies with intact or debrided corneas demonstrating corneal penetration measured by adequate aqueous humor concentration levels of ganciclovir gel 0.15%. Given the penetration data, topical antivirals (ganciclovir and trifluridine) may not be useful in the treatment of deeper herpes simplex keratitis infections, especially when the corneal epithelium is intact.

SUPPORT DOCUMENT IV: Combining Antiviral Agents

There is insufficient evidence to conclude that the combination of two antiviral agents treats HSV epithelial keratitis more effectively than a single antiviral agent.[1-3]

Topical acyclovir plus topical vidarabine performed as well as topical acyclovir alone for the treatment of dendritic HSV epithelial keratitis in one randomized double blind placebo controlled trial.[2] Oral acyclovir plus idoxuridine ointment healed ulcers more quickly than idoxuridine ointment alone in one clinical trial without randomization, masking, or placebo control.[1] In the HEDS Epithelial Keratitis trial, The HEDS Group aimed to evaluate the efficacy of oral acyclovir in preventing stromal keratitis or iritis in patients with HSV epithelial keratitis.[3] In this study, patients with HSV epithelial keratitis were treated with topical trifluridine alone or in combination with a three week course of oral acyclovir 400 mg five times daily. A secondary outcome to this study (without statistical analysis) compared the ability of these two treatment modalities to resolve HSV epithelial keratitis. It appears that patients treated with topical trifluridine alone experience corneal ulcer healing just as quickly as patients treated with a combination of trifluridine solution and oral acyclovir. This was a secondary outcome to the study and lacked any statistical analysis making it difficult to assess the value of the observation. Additionally, the two aforementioned studies compared antiviral agents that are no longer used, idoxuridine[1] and vidarabine,[2] making it difficult to extrapolate to the antiviral agents used today; thus reducing the value of these results.

1. Srinivas C. Combination therapy of acyclovir and idurine in herpetic keratitis. Afro-Asian Journal of Ophthalmology 1993;12:336-7.
2. Colin J, Chastel C, Kaufman HE, Kissling GE. Combination therapy for dendritic keratitis with acyclovir and vidarabine. J Ocul Pharmacol 1987;3:39-42.
3. HEDS. A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex virus epithelial keratitis. The Epithelial Keratitis Trial. The Herpetic Eye Disease Study Group. Arch Ophthalmol 1997;115:703-12.

SUPPORT DOCUMENT V: Interferon Treatment of HSV Epithelial Keratitis

Interferon Monotherapy: Epithelial Keratitis

Interferon at sufficient concentration has antiviral activity against HSV infected epithelial cells. Interferon, used either alone or in combination with debridement,[1-3] appears as effective as a nucleoside antiviral agent. Combined interferon-antiviral therapy does not differ from antiviral monotherapy at two weeks of treatment, but the combination of interferon and an antiviral agent may enable faster healing.

1. Cantell K. Development of antiviral therapy with alpha interferons: promises, false hopes and accomplishments. Ann Med 1995;27:23-8.
2. Sundmacher R. Interferon in ocular viral diseases. Interferon 1982;4:177-200.
3. Sundmacher R, Cantell K, Mattes A. Combination therapy for dendritic keratitis. High-titer alpha-interferon and trifluridine. Arch Ophthalmol 1984;102:554-5.

SUPPORT DOCUMENT VI: Literature Search Details

SEARCH #1

Pubmed Search: Through October 29, 2010

(((((("herpetic keratitis")) OR ("stromal keratitis") OR ("disciform keratitis") OR ("herpetic eye disease")) OR ("herpes simplex eye disease") AND (English[lang])) OR ("Keratitis, Herpetic"[Mesh] AND (English[lang]))) NOT ("Herpes Zoster Ophthalmicus"[Mesh] AND (English[lang]))

[with filters on Human / Eng / PDat up to 2010 Oct 29]

Cochrane [EBSCO]: Up to September 30, 2010

((herpes OR herpetic) AND keratitis) OR "herpetic eye disease" OR "herpes simplex eye disease" OR "stromal keratitis" OR "disciform keratitis"

EMBASE: 1900 to 2010

'herpes simplex keratitis'/exp OR 'herpetic eye disease' OR 'herpes simplex eye disease' OR 'stromal keratitis' OR 'disciform keratitis' AND [humans]/lim AND [english]/lim

SEARCH #2

Pubmed Search: October 29, 2010 through July 11, 2013

[After Oct 29 2010 including stromal and disciform]

(((((("herpetic keratitis")) OR ("stromal keratitis") OR ("disciform keratitis") OR ("herpetic eye disease")) OR ("herpes simplex eye disease") AND (English[lang])) OR ("Keratitis, Herpetic"[Mesh] AND (English[lang]))) NOT ("Herpes Zoster Ophthalmicus"[Mesh] AND (English[lang]))

Filter Human / Eng / PDate after Oct 29 2010

Cochrane [EBSCO]: October 1, 2010 through July 11, 2013

((herpes OR herpetic) AND keratitis) OR "herpetic eye disease" OR "herpes simplex eye disease" OR "stromal keratitis" OR "disciform keratitis"

EMBASE: 2011 through July 11, 2013

'herpes simplex keratitis'/exp OR 'herpetic eye disease' OR 'herpes simplex eye disease' OR 'stromal keratitis' OR 'disciform keratitis' AND [humans]/lim AND [english]/lim