

# Practice patterns for herpes simplex keratitis: A survey of ophthalmologists in Gulf Coast countries



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## Abstract

**Purpose:** Herpes simplex is a common cause of visual disability, and there are published evidence-based guidelines for therapy. This survey aims to determine the preferred practice patterns of ophthalmologists in Gulf Coast Countries regarding herpetic eye disease, as well as identify areas of controversy or barriers to acceptance of evidence-based protocols.

**Methods:** Anonymous web-based survey of ophthalmologists in Saudi Arabia, Bahrain, the United Arab Emirates, and Oman.

**Results:** There were 48 responses to the survey. For a first episode of epithelial dendritic keratitis, 28.2% reported “observation” rather than specific therapy. The majority of respondents utilize oral or topical antiviral for epithelial keratitis, with oral antiviral being the most popular (43.6%). The majority also included a corticosteroid with antiviral for stromal keratitis (83.9%) or iritis (70.3%). Over 90% prescribe a prophylactic antiviral after keratoplasty for herpetic eye disease, although the length of therapy ranged widely from <6 months to indefinite. The perceived risk of recurrent disease was ranked as the most important factor when considering antiviral prophylaxis, followed by risk of adverse effects. Topical cyclosporine was utilized “never or almost never” by 76.9% of respondents.

**Conclusions:** Most respondents report following evidence-based guidelines. There was less consensus in areas where there are remaining knowledge gaps, such as the length of antiviral prophylaxis after keratoplasty and the potential role for topical cyclosporine.

**Keywords:** Herpes simplex, Keratitis, Stromal keratitis, Practice pattern, Antiviral, Survey

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## Introduction

Herpes simplex virus (HSV) causes muco-cutaneous infections in humans that are characterized by multiple recurrences, as the virus travels through sensory neurons to the nearest sensory ganglion and remains latent there for the lifetime of the host.<sup>1</sup> Ocular infections are commonly caused by HSV type-1, and can range from epithelial keratitis to keratouveitis and retinitis. The annual incidence of HSV ocular infections in the USA is estimated to be 59,000 new and recurrent cases, the majority being keratitis.<sup>2</sup> In France the incidence of HSV keratitis was estimated to be 31.5 per

100,000 annually<sup>3</sup> but no similar epidemiologic data are available for Gulf Coast Countries (GCC).

Clinical manifestations are typically presumed to be due to reactivation of the latent virus, as the primary infection may be asymptomatic or cause mild self-limited conjunctivitis.<sup>4</sup> Patients with HSV keratitis may complain of conjunctival injection, pain, watery discharge and foreign body sensation. The diagnosis of HSV keratitis is often clinically based on history and examination findings without the need for confirmatory tests. Clinical findings include characteristic dendritic corneal epithelial findings in case of epithelial keratitis, or corneal edema and infiltrates in case of stromal keratitis.

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There are many plausible approaches to the treatment of HSV ocular infections. Topical and systemic antiviral medications, corticosteroids and wiping debridement have been suggested and used in the treatment of the different kinds of HSV keratitis.

In order to create an evidence-based foundation for the treatment of HSV keratitis, a systematic review concluded that topical trifluridine and acyclovir were very effective in the treatment of acute HSV epithelial keratitis, whereas adding corticosteroids to an antiviral was effective for HSV stromal keratitis; long-term treatment with oral acyclovir was recommended to reduce recurrences in those patients at higher risk for vision loss, such as those with stromal keratitis.<sup>5</sup> According to the Herpetic Eye Disease Study, oral acyclovir was associated with a significant decrease in the recurrence of both types of keratitis during the one year duration of the study.<sup>6</sup> Ocular or systemic corticosteroids appear to be beneficial for treating HSV keratouveitis with a concomitant antiviral.<sup>7</sup>

Keratoplasty is sometimes indicated to regain vision in patients with severely opacified corneas secondary to HSV stromal keratitis. In addition to an immunosuppressive drug (such as topical corticosteroids) to prevent allograft rejection, systemic antiviral treatment is usually given to patients following keratoplasty for herpetic eye disease to prevent recurrence of the latent infection. One small prospective study evaluated the effect of acyclovir on the outcome of penetrating keratoplasty (PKP) for HSV; they reported a decrease in recurrences of HSV among those patients receiving a longer course of therapy (3 weeks compared to 1 year).<sup>8</sup> The timing of surgery may also play a role in the prognosis, as performing keratoplasty in a scarred, non-inflammatory state may result in a better prognosis.<sup>9</sup>

While many studies provide a strong evidence base for antiviral prophylaxis, little is known about the natural history of latent HSV after discontinuation of antiviral therapy. In patients undergoing PKP for HSV, oral acyclovir 400 mg twice daily for six months was associated with a decrease in the recurrence of herpetic eye disease during a 2 year follow-up period.<sup>10</sup> Another study found that the recurrence rate of herpetic eye disease following PKP was significantly lower in a group of patients that received Acyclovir for the first six months after the surgery in comparison with a placebo group during a 5 year follow-up period.<sup>11</sup>

Ophthalmologists in the United Kingdom were surveyed in order to evaluate the clinical practice for primary epithelial and stromal HSV keratitis, in addition to the use of prophylactic oral antiviral treatment for recurrent disease. Results were compared with published Herpetic Eye Disease Study (HEDS) guidelines, and concluded that their treatment patterns were consistent with HEDS guidelines in treating primary epithelial and stromal HSV keratitis. However, some deviation was observed in the prophylactic management of recurrent disease, especially among non-cornea specialists. They concluded that dissemination of such results would help in improving prophylactic treatment of recurrent HSV keratitis.<sup>12</sup>

The current practice patterns of ophthalmologists practicing in Saudi Arabia and other Gulf Coast countries are unknown. The patient populations and healthcare systems vary in important ways from those studied in the HEDS and other prospective trials; studying the practice patterns in the Arab world may shed light on unique treatment

approaches and help determine whether there are barriers to implementing evidence-based guidelines.

## Methods

This was a web-based survey targeting both general ophthalmologists and cornea subspecialists of GCC countries. This study was performed with the approval of the Institutional Review Board of the King Khaled Eye Specialist Hospital, and adhered to the tenets of the Declaration of Helsinki.

A self-administered anonymous web-based survey was conducted using a questionnaire having 14 closed-ended questions. We enquired about the recipient's preferred practice patterns (PPP) regarding the treatment of primary and recurrent HSV (epithelial keratitis, stromal keratitis and keratouveitis), and the use of oral antiviral prophylaxis in patients treated with keratoplasty.

In order to encourage a better response rate we described the objectives and the value of this type of study, without specifically discussing the evidence-based measures being surveyed. The initial question was asked for the participant's consent to participate; those who answered "no" were excluded. The data management was carried out with transfer of the web-based spreadsheet into Statistical Package for Social Studies (SPSS v22, IBM corp, Armonk NY). Descriptive data are reported as percentages with 95% confidence intervals.

## Results

### Demographics

Forty-eight physicians responded to the survey; the survey results are summarized in [Table 1](#). The majority of our survey respondents were practicing ophthalmologists (83%). Of all respondents, 41% of them were cornea/anterior segment specialists and 46% reported another ophthalmology subspecialty; the remaining 12% were general ophthalmologists.

### Current practice patterns

In treating the first episode of epithelial (dendritic) herpes simplex keratitis, most respondents chose prescribing systemic antiviral treatment (acyclovir, valacyclovir, or famciclovir). When all forms of topical therapy were combined, 11 (28.2%) of respondents selected this form of therapy.

When treating the first episode of herpes simplex stromal keratitis, the most common chosen answer was topical corticosteroids and antiviral. Similarly, most respondents chose to treat the first episode of herpes simplex endotheliitis or iritis with topical corticosteroid and antiviral. No respondents selected topical corticosteroid alone for either stromal keratitis or iritis. Most physicians reported not using topical cyclosporine for herpes simplex stromal keratitis.

A systemic antiviral (acyclovir, valacyclovir, or famciclovir) was the preferred prophylactic treatment for recurrent epithelial and stromal keratitis. For patients who have undergone keratoplasty, systemic antiviral was the preferred prophylaxis treatment by most of the respondents as well. Approximately 90% of respondents used oral antiviral for at least 6 months after keratoplasty in herpes simplex patients.

Physicians were asked to rank in order of importance of some factors that may influence their decision to recommend

**Table 1.** Results of survey.

Questions and choices	(n)	CI
1. Are you a practicing ophthalmologist?		
Yes	(41) 83.7%	
No	(7) 14.3%	(8.526–31.26)
2. What is your highest level of training?		
Ophthalmology Residency	(5) 12.8%	(5.324–25.54)
Fellowship in Anterior Segment/Cornea	(16) 41%	(25.66–54.27)
Fellowship in other subspecialty	(18) 46.2%	(29.89–58.96)
3. How do you treat the first episode of epithelial (dendritic) herpes simplex keratitis?		
Observation	(11) 28.2%	(15.7–41.93)
Wiping debridement	(0) 0%	(0–8.566)
Topical Ganciclovir	(3) 7.7%	(2.52–19.43)
Topical Acyclovir	(6) 15.4%	(6.885–28.44)
Systemic Antiviral (acyclovir, valacyclovir, or famciclovir)	(17) 43.6%	(27.76–56.63)
Topical corticosteroids and antiviral	(2) 5.1%	(1.248–16.14)
4. If a patient has recurrent episodes of epithelial keratitis, what prophylactic treatment do you recommend (after treatment of the acute episode)?		
Observation	(11) 29.7%	(15.7–41.93)
Topical Ganciclovir	(3) 8.1%	(2.52–19.43)
Topical Acyclovir	(6) 16.2%	(6.885–28.44)
Systemic Antiviral (acyclovir, valacyclovir, or famciclovir)	(17) 45.9%	(27.76–56.63)
5. How do you treat the first episode of herpes simplex stromal keratitis?		
Observation		
Topical Ganciclovir	(2) 5.4%	(1.248–16.14)
Topical Acyclovir	(1) 2.7%	(0.4319–12.59)
Systemic Antiviral (acyclovir, valacyclovir, or famciclovir)	(3) 8.1%	(2.52–19.43)
Topical corticosteroid alone	(0) 0%	(0–8.566)
Topical corticosteroid and antiviral	(31) 83.9%	(60.66–86.17)
6. If a patient has recurrent episodes of stromal keratitis, what prophylactic treatment do you recommend (after treatment of the acute episode)?		
Observation	(2) 5.4%	(1.248–16.14)
Topical Ganciclovir	(1) 2.7%	(0.4319–12.59)
Topical Acyclovir	(1) 2.7%	(0.4319–12.59)
Systemic Antiviral (acyclovir, valacyclovir, or famciclovir)	(25) 67.5%	(45.73–74.34)
Topical corticosteroid alone	(0) 0%	(0–8.566)
Topical corticosteroid and antiviral	(8) 21.6%	(10.23–34.01)
7. Do you use topical Cyclosporine for herpes simplex stromal keratitis?		
Almost always	(2) 5.1%	(1.248–16.14)
>50% of the time	(6) 15.4%	(6.885–28.44)
<50% of the time	(1) 2.6%	(0.4319–12.59)
Never or almost never	(30) 76.9%	(58.07–84.3)
8. How do you treat the first episode of herpes simplex endotheliitis or iritis?		
Observation		
Topical Ganciclovir	(0) 0%	(0–8.566)
Topical Acyclovir	(2) 5.4%	(1.248–16.14)
Systemic Antiviral (acyclovir, valacyclovir, or famciclovir)	(9) 24.3%	(12–36.7)
Topical corticosteroid alone	(0) 0%	(0–8.566)
Topical corticosteroid and antiviral	(26) 70.3%	(48.12–76.41)
9. After keratoplasty (for an eye with previous herpes simplex keratitis), what is your preferred post-operative antiviral prophylaxis?		
Observation	(3) 9.7%	(2.52–19.43)
Topical Ganciclovir	(1) 3.2%	(0.4319–12.59)
Topical Acyclovir	(5) 16.1%	(5.324–25.54)
Systemic Antiviral (acyclovir, valacyclovir, or famciclovir)	(22) 70.9%	(53.41–83.9)
10. If you utilize antiviral prophylaxis after keratoplasty, what is your typical length of therapy?		
<6 months	(3) 9.7%	(2.52–19.43)
6 months-1 year	(13) 41.9%	(26.42–59.23)
>1 year or until off of topical corticosteroids	(12) 38.7%	(23.73–56.17)
Indefinite- lifetime	(3) 9.7%	(2.52–19.43)

antiviral prophylaxis for their patients. The risk of recurrence was ranked as being the most important factor, and the risk of adverse effects was ranked second followed by the convenience for patients; the cost of therapy was ranked as the least important factor to consider when prescribing antiviral prophylaxis.

## Discussion

The treatment of herpetic eye disease has been refined by the results of prospective randomized controlled trials, such as the HEDS studies. However, there are many plausible reasons for practice patterns to deviate from the protocols as

described in the landmark clinical trials. The results may not be generalizable to all patients with a given disease, newer treatments may become available (if supported by sufficient evidence of equivalence or superiority), or specific patient or healthcare system factors dictate an alternate therapeutic approach. This survey is an initial attempt to define the common practice patterns of ophthalmologists in GCC who treat herpetic eye disease; in general, most respondents are following evidence-based guidelines as published in the HEDS and other prospective randomized controlled trials. For example, no respondents reported utilizing corticosteroids in the absence of a concomitant antiviral. The majority of respondents reported utilizing some types of antiviral prophylaxis for patients with recurrent stromal keratitis, a disease with a high risk for vision loss if untreated. However, there are some important differences that deserve further study. For example, almost 10% of respondents reported "observation only" after keratoplasty in patients with previous herpes stromal keratitis; this opinion (if not related to survey respondent error) is difficult to justify, as systemic therapy and topical therapy are relatively benign with proven efficacy and a low rate of adverse effects.

Several of the questions posed to the respondents do not have known "best" answers supported by level 1 data; for example, the ideal length of antiviral prophylaxis after keratoplasty remains up for debate. It is assumed that indefinite prophylaxis will decrease the risk of recurrent disease, but there are no long-term studies to quantify the reduction in risk if patients are maintained on therapy beyond one year. This is reflected in the responses; approximately 40% selected 6–12 months of therapy after keratoplasty and 40% selected ">1 year or until off of topical corticosteroids". Only 10% selected "indefinite- lifetime", presumably reflecting the lack of efficacy data beyond the initial postoperative years. This is a knowledge gap that requires further study. Regarding topical cyclosporine for stromal keratitis, there are no prospective controlled trials to support its use, although it may be beneficial.<sup>13</sup>

In what may be a reflection of the healthcare systems in which the respondents practice, cost of therapy was the least important factor when deciding whether or not to recommend antiviral prophylaxis. The risk of disease recurrence was deemed to be most important, balanced by the risk of adverse effects of the medication.

## Conclusions

In summary, the evidence-based treatment of herpetic eye disease continues to evolve, and this survey suggests that the majority of ophthalmologists in the GCC are following the published literature. Several important questions remain,

and as future studies fill these knowledge gaps and clarify the best therapeutic options, we anticipate the practice patterns will evolve accordingly.

## Conflict of interest

Authors declare that there is no conflict of interest.

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