

PREFERRED PRACTICE PATTERN®
CLINICAL QUESTIONS



**Herpes Simplex
Virus Epithelial
Keratitis**

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HSV PPP Clinical Question

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Preferred Practice Pattern® (PPP) Clinical Questions are evidence-based statements that guide clinicians in providing optimal patient care. PPP Clinical Questions answer specific questions in the "Patient, Intervention, Comparison, Outcome" (PICO) format.

PPP Clinical Questions are developed by the Academy's H. Dunbar Hoskins Jr., M.D. Center for Quality Eye Care without any external financial support. Authors and reviewers of PPP Clinical Questions are volunteers and do not receive any financial compensation for their contributions to the documents.



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Methods and Key to Ratings

Preferred Practice Pattern Clinical Questions 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 Network¹ (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation² (GRADE) group are used. 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 SIGN¹ is 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

SIGN¹ 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) |

GRADE² 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 |

GRADE² 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 |



PPP Clinical Question

TOPIC

Herpes simplex virus epithelial keratitis

CLINICAL QUESTION

How do therapeutic interventions for patients with active HSV dendritic epithelial keratitis compare for healing of the corneal epithelium?

LITERATURE SEARCH

The literature search for the Cochrane Review was last updated in October 2010. To present this Clinical Question, a literature search was undertaken in January 2012 for the intervening period.

[Literature search details](#)

SYSTEMATIC REVIEW

Wilhelmus KR. [Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis](#). Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD002898. DOI: 10.1002/14651858.CD002898.pub4.



Recommendations for Care

SUMMARY

The topical agent trifluridine and newer antiviral agents acyclovir, brivudine, and ganciclovir, are efficacious treatments for Herpes simplex virus (HSV) epithelial keratitis. Oral antiviral agents are efficacious treatments for HSV epithelial keratitis; additional data would help to adequately assess their beneficial effects when used either adjunctively or alone. The combined treatment of interferon and an antiviral agent may speed the healing process and may be appropriate for recalcitrant cases. Debridement is an alternative treatment to chemotherapeutic drugs, but it is more efficacious when followed by antiviral treatment.

(Moderate Quality, Strong Recommendation)

DISCUSSION

Epithelial keratitis is the most prevalent form of HSV, accounting for 50% to 80% of ocular herpes cases. Worldwide, approximately 1 million cases of new or recurrent HSV epithelial keratitis occur each year. Without treatment, only half of herpetic corneal surface infections heal within 2 weeks. Controversy remains as to what treatment is the most efficacious in treating HSV epithelial keratitis. (Note: The distinction between HSV and herpes zoster epithelial keratitis can be difficult for clinicians unfamiliar with these conditions. Accurate diagnosis is important in the guidance of treatment, i.e. corticosteroids versus no corticosteroids.)

Topical Antiviral Agents

Topical antiviral agents trifluridine, acyclovir, brivudine, and ganciclovir were almost equally efficacious in treating epithelial keratitis, helping 90% of the total corneas treated in 52 studies to heal within 2 weeks. Formulations or dosages of topical antiviral agents were rarely compared in the studies. Acyclovir and brivudine appear to be similar in efficacy and were not significantly different from trifluridine. While use of ganciclovir was associated with a better outcome than acyclovir, similar healing rates were found at 7 days. The ganciclovir/acyclovir comparison was limited by insufficient data. The benefit of using a second antiviral agent, either topical or oral, is unclear.

Forty of the 88 trials that examined topical antivirals reported adverse reactions from antiviral use. Adverse reactions from topical antivirals included stinging upon installation, allergic blepharoconjunctivitis,

superficial keratopathy, and toxo-allergic follicular conjunctivitis. Among the trials that resulted in adverse reactions, the median percentage of eyes that resulted in superficial keratopathy or punctate epithelial erosions was as follows: acyclovir, 10%; ganciclovir, 4%; trifluridine, 4%; and brivudine, 0%. However, because the number of studies and number of participants varied for each drug, these figures do not accurately depict the safety of the antivirals.

Oral Antiviral Agents

The use of oral acyclovir alone was found to be as efficacious as topical antiviral therapy. The role of oral acyclovir in treating herpetic eye disease is consistent with the findings of evidence-based reviews on the episodic dosing of oral antivirals for labial or genital herpes.

Few trials compared the healing rates of combined oral and topical antiviral treatment to topical antiviral therapy alone. Among those that did, oral antiviral therapy used in conjunction with topical acyclovir was as efficacious – but not more efficacious – than topical antiviral treatment alone.

Topical Interferon Therapy

Topical interferon therapy was shown to be as efficacious as antiviral agents, both when used alone and when used in conjunction with debridement. While few studies compared different types or formulations of interferon, higher interferon concentrations were generally shown to be more efficacious than lower concentrations – those below 1 million IU/ml. However, studies could not clearly demonstrate a dose-response relationship for progressively increasing interferon dosages. The form of interferon – interferon- α , interferon- β , recombinant interferon, or naturally derived interferon – did not result in any differences in efficacy.

Interferon-Antiviral Combination Therapy

Studies of interferon-antiviral combination treatments were inconsistent, possibly because interferon concentrations varied by study. Interferon-antiviral combination therapy was not significantly better than use of antiviral agents alone at 14 days, but evidence suggests earlier and faster healing using interferon-antiviral combination therapy compared to antiviral monotherapy. Data on the safety of interferon therapy was not provided.

Debridement

Corneal epithelial debridement was found to be more efficacious when followed by use of an antiviral agent or interferon, although the efficacy of this treatment remains inconclusive due to trial heterogeneity on healing rates and no discernible difference in healing rates at the two-week mark compared to antiviral monotherapy. The risks of debridement – damaging the Bowman’s layer or causing further corneal inflammation or scarring – have been debated for years, but there is currently no evidence to support these claims.

Supplemental Agents

There is inadequate evidence indicating the efficacy of a cytokine growth factor or nonsteroidal anti-inflammatory drug following antiviral therapy; the usefulness of other immunomodulators remains unclear.

Prolonged Epithelial Defects in HSV

Prolonged epithelial defects in HSV epithelial keratitis may occur as a result of the inhibitory effect of inflammatory cells on corneal epithelial wound healing, as suggested by prolonged healing noted in the setting of peripheral lesions and in those with underlying stromal inflammation. Other causes of prolonged epithelial defects include epithelial toxicity from topical antiviral agents and virological resistance to the therapeutic agent. HSV strains that are not readily susceptible to acyclovir and other antivirals are becoming increasingly prevalent, and may require the selection of an alternative antiviral for treatment. Viral resistance may develop in immunocompromised patients – including patients with bone marrow transplants, cancer, or AIDS – and in patients with intermittent antiviral therapy. Secondary bacterial infections rarely occur.

Healing corneal epithelial defects can result in epithelial abnormalities that may be confused with HSV epithelial keratitis. Eyes with recurrent erosion syndrome may have epithelial irregularities that resemble HSV dendrites, but also often have a history of multiple recurrences that may mimic HSV epithelial keratitis.



References

1. Scottish Intercollegiate Guidelines Network. SIGN 50: a guideline developer's handbook. Available at: www.sign.ac.uk/methodology/index.html. Accessed May 15, 2012.
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.
3. GRADE Working Group. Organizations that have endorsed or that are using GRADE. Available at: www.gradeworkinggroup.org/society/index.htm. Accessed May 15, 2012.