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Management of Herpes Simplex Virus Keratitis

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Management of Herpes Simplex Virus Keratitis in the Pediatric Population

Saujanya Vadoothker, MD, Laura Andrews, MD, Bennie H. Jeng, MD, and Moran Roni Levin, MD

Abstract: Herpes simplex virus (HSV) keratitis is a highly prevalent and visually disabling disease in both the pediatric and adult population. While many studies have investigated the treatment of HSV keratitis in adult patients, few have focused on managing this condition in children. Children are at particularly high risk for visual morbidity due to unique challenges in diagnosis and treatment, and the often more aggressive disease course that results in corneal scarring, and subsequently amblyopia. This review presents the pathogenesis and most current recommendations for the medical and surgical management of HSV keratitis in the pediatric population.

Key Words: herpes simplex virus keratitis, viral keratitis, pediatric eye disease

Compared with adults, children have overall worse visual outcomes associated with HSV keratitis and require more frequent monitoring. Ocular examination of children poses unique challenges, and difficulty with examination leads to higher rates of misdiagnosis and treatment delays.² Children also develop more severe disease manifestations including bilateral HSV keratitis and more frequent recurrences, leading to corneal stromal scarring.³⁻⁶ Unlike adults, children are at risk for permanent vision loss from amblyopia if stromal scarring occurs. This review focuses on the pathogenesis, diagnosis, and medical and surgical management of HSV keratitis in the pediatric population.

in HSV keratitis.^{3,7} The virus may become latent in the sensory ganglia and reactivate causing recurrent episodes of ocular inflammation.⁷ Risk factors for reactivation include incisional or laser eye surgery, trauma, atopic disease, diabetes, and immune compromise.⁷ Stromal scarring and neovascularization occur in response to invasion of the cornea by polymorphonuclear leukocytes and the release of inflammatory cytokines, which incite deposition and remodeling of the extracellular matrix. Angiogenesis from viral disruption of both pro and anti-angiogenic factors such as vascular endothelial growth factor (VEGF) and thrombospondin 1 and 2, respectively, may begin as early as 24 hours postinfection.^{4,7}

EPIDEMIOLOGY

HSV-1 and 2 have a seroprevalence of 50–90% across the general population, including both adults and children.^{2,3} Seroprevalence rates differ across socioeconomic groups with approximately 30% higher rates among children under 5 in lower socioeconomic conditions compared with children in the middle socioeconomic class.^{3,5}

PATHOGENESIS

Both HSV-1 and 2 can cause ocular infection; however, HSV-1 occurs more often in the eye. HSV-1 is a linear double stranded DNA virus that spreads through direct contact with active lesions or infected secretions.^{3,7} Infection results from direct cell-to-cell inoculation and spreads via peripheral sensory nerves to the trigeminal ganglion

CLINICAL PRESENTATION

Symptoms of HSV keratitis in children include tearing, burning, decreased vision, swollen eyelids, and photophobia. Up to two-thirds of primary HSV infections do not cause symptoms or are unrecognized by patients or caregivers.^{3,5} Furthermore, children may not report ocular symptoms reliably and can be challenging to thoroughly examine, often causing a delay in presentation to a specialist up to 30 days.⁵ Unfortunately, HSV keratitis is frequently misdiagnosed in children (15–30%) and, thus, inadequately treated.^{2,4,5}

Corneal herpetic disease can be divided into epithelial keratitis, stromal keratitis, and endothelial keratitis, depending on the layer of cornea affected by the disease (figure 1).^{3,4,7} Corneal epithelial disease starts

Accepted for publication May 2, 2018.

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The authors have no funding or conflicts of interest to disclose.

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ISSN: 0891-3668/18/3709-0949

DOI: 10.1097/INF.0000000000002114

The ESPID Reports and Reviews of *Pediatric Infectious Disease Journal* series topics, authors and contents are chosen and approved independently by the Editorial Board of ESPID.

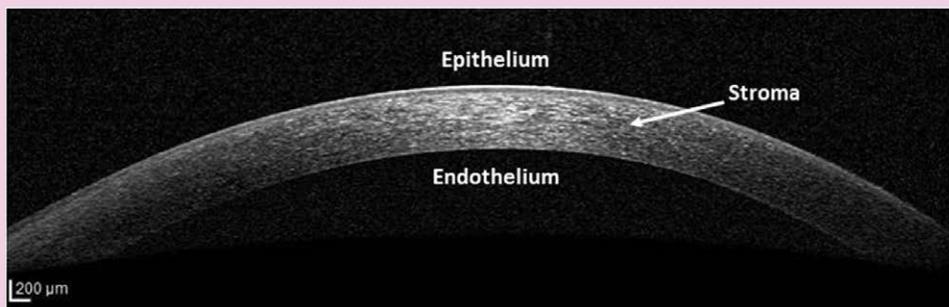


FIGURE 1. Optical coherence tomography depicting the layers of the cornea (Photo credit: William Buie).

as a painful punctate epithelial keratopathy that progress to dendritic epithelial ulcers or geographic ulcers. Up to 76% of children with HSV keratitis develop damage to the corneal nerves leading to decreased corneal sensation and neurotrophic keratitis, contributing to corneal scarring.^{5,6}

Stromal keratitis falls into 2 categories. The less severe nonnecrotizing infection is an immune-mediated reaction to viral antigens, which may occur without a history of epithelial disease. It is characterized by inflammation of the corneal stroma and infiltration with leukocytes. Longstanding or recurrent disease is associated with corneal neovascularization and lipid deposition. Conversely, necrotizing stromal keratitis is due to active viral infection with overlying epithelial ulceration and can result in corneal thinning and perforation requiring emergent surgical intervention.⁷ Children have a 35–50% chance of developing stromal keratitis due to an increased inflammatory response.^{4–7}

Rare in children, endothelial keratitis is classified as disciform (disc shaped area of corneal edema with thickening and opacification), diffuse, or linear. Corneal opacification results from damage to corneal endothelial cells that regulate corneal water content.⁷

Current studies differ widely on the prevalence of bilateral herpetic keratitis in children, which is reported from 0% to 26%.^{4–6} While bilateral adult disease has been associated with atopy and immune suppression, this relationship remains unclear in the pediatric population. Recurrent disease is more common in children than adults and can occur in 38–80% of infected patients, usually 12–15 months after initial infection.^{2,4–6} No definite risk factors have been demonstrated for recurrent disease, although 1 study suggested an increased rate of recurrence in females.^{5,6}

DIAGNOSIS

Although HSV keratitis is usually diagnosed based on clinical appearance, several ancillary tests can be used to aid in diagnosis. Viral culture remains the gold

standard, but presents several challenges, making this test impractical for clinical use: viral cultures have low sensitivity, samples must be obtained early in symptom onset, and results take up to 10 days. Direct fluorescent antibody testing has good sensitivity and specificity but is expensive and less available.^{2,3} DNA amplification using polymerase chain reaction is sensitive and specific, and quantitative real-time polymerase chain reaction may be used to differentiate between physiologic and pathologic viral shedding. Other testing includes the Tzank smear, in which scrapings are stained and examined under light microscopy for multinucleated giant cells with eosinophilic Cowdry Type A inclusion bodies. Serum antibody testing is available but less useful because it cannot detect recurrent infection.³ Due to the difficulty in performing testing in children where presentation is often delayed, the usefulness of clinical testing is limited. Clinicians generally rely on the clinical presentation and examination to formulate a treatment regimen.

MANAGEMENT

Medical management with topical or oral antiviral agents is the mainstay of treatment for HSV keratitis. Topical medications currently available in the United States and Europe include trifluridine and ganciclovir, and current oral antivirals include acyclovir, valacyclovir and famciclovir. In addition to the above medications, acyclovir 3% ophthalmic ointment is available and approved for topical use in Europe.³

While large, randomized, controlled trials have not been performed with regard to HSV keratitis in children, the Herpetic Eye Disease Study, a multi-center, multi-armed set of randomized and placebo controlled trials in patients 12 and older, sets the baseline for determining epidemiology, treatment and prophylaxis for HSV keratitis.³ Current studies extrapolate from this data, and therefore, oral acyclovir was determined to be the best treatment method in children. Studies have proven acyclovir safe in children for

neonatal herpes, and oral therapy has been well-tolerated.^{1,2,4,5,8} Treatment for epithelial keratitis is oral acyclovir. For nonnecrotizing stromal keratitis or endotheliitis, topical steroids are recommended in addition to oral acyclovir. Steroids are not recommended for necrotizing stromal keratitis due to the active viral disease that could be worsened with its use. The recommended dosing of acyclovir in children is 12–20 mg/kg/day.^{2,4} Kidney and liver function should be checked biannually for children using oral anti-virals.¹ Up to 25% of cases with HSV epithelial keratitis resolve spontaneously.^{2,7} On average, active and recurrent HSV epithelial keratitis achieves full resolution in approximately 17 and 28 days.³

Once the disease has gone into remission, patients should be observed for recurrence. The Herpetic Eye Disease Study trial found that acyclovir prophylaxis of 400 mg twice a day for 1 year significantly reduces the recurrence of epithelial and stromal keratitis; however, no set dose has been established for prophylaxis in children.⁹ If a recurrence occurs, acyclovir is restarted until the active disease resolves.^{6,8} If no recurrences occur during the year of prophylaxis, then acyclovir can be discontinued, and patients may be monitored closely for disease reactivation. Indefinite therapy with oral acyclovir is warranted for multiple recurrences, and previous recurrences increase the risk for future recurrence. Pediatric patients have a tendency toward increased corneal neovascularization and stromal scarring likely due to a strong immune reaction to the virus; thus, the disease can recur despite suppressive therapy. In these cases, dosing adjustments should be made as children grow.^{2,4}

Acyclovir resistance may be seen in patients with severe disease who are taking acyclovir for long periods of time, especially when using topical steroids. Prolonged topical steroid treatment has been found to create an environment favorable to breeding resistant strains.^{2,9} More resistant strains are found in immunocompromised patients, and resistance is enhanced due to patient noncompliance. In these cases, we recommend starting

combination therapy with both a systemic and new topical antiviral to combat resistance.⁹

Surgical treatment with a penetrating keratoplasty (full thickness corneal transplant) offers a possibility of visual recovery for patients with significant corneal scarring or neovascularization. Potential surgical complications include ocular hypertension, glaucoma, graft rejection, recurrence of the virus in the graft and graft failure. Neovascularization in particular puts the new graft at higher risk for rejection. Visual outcomes of surgery vary between 20/20 visual acuity to light perception vision.¹ Postoperative management may be complicated by inflammation, poor patient cooperation and follow-up and limited communication—all creating potential barriers to a good surgical outcome. Studies recommend prophylactic acyclovir therapy after surgery to prevent a recurrence in the new tissue.

Long-term complications of herpetic eye disease in children include recurrence (50%), corneal scarring (80%) and corneal neovascularization (> 30%). Deprivation amblyopia may be caused by corneal opacification and refractive amblyopia may be caused by increased astigmatism greater than 2 diopters (25%).^{4,6} The incidence of amblyopia in children with HSV keratitis has been reported between 33% and 80%.⁵ Refractive correction and amblyopia treatment with patching of the better seeing eye should be initiated early and are essential to maximize visual recovery.^{4,6}

The treatment of HSV keratitis can be particularly challenging. Crying during topical drop administration (diluting drops

and reducing medication efficacy), skipping doses or prematurely stopping medication can lead to inadequate treatment.⁸ It is essential that the treating physician and caregivers work as a team to improve adherence to treatment.

FUTURE CONSIDERATIONS

While this review focuses on the current treatment of herpetic keratitis in children, experimental studies are investigating new treatments for this disease. Targeted drug delivery methods that can improve topical administration of medical therapy including monoclonal antibodies, topical and subconjunctival injections of anti-HSV IgG fab fragment AC-8 and intrastromal injections of DNA plasmids containing inflammatory and anti-angiogenic modulators are being studied.² Anti-VEGF monoclonal antibody fragments, currently used for the treatment of retinal neovascularization, are now being explored for use in corneal neovascularization.² Anti-HSV IgG AC-8 fragments have been shown to decrease viral titers and treating clinical disease with less epithelial toxicity in mice but also have been found less effective than trifluridine.² DNA plasmids containing anti-VEGF and interleukin-18 (VEGF regulator) have also reduced angiogenesis resulting from HSV-1 infection. Currently, no clinical trials exist for gene therapy for HSV keratitis in humans.²

CONCLUSION

This review aims to summarize the pathogenesis, clinical findings, diagnosis and management of pediatric herpetic

keratitis based on the limited studies available in the current literature. Further research will improve our understanding of the treatment of HSV keratitis in the pediatric population. A challenge for patient care, this disease requires diligence on the part of all involved to prevent significant visual morbidity in this population.

REFERENCES

1. Serna-Ojeda JC, Loya-Garcia D, Navas A, et al. Long-term outcomes of pediatric penetrating keratoplasty for herpes simplex virus keratitis. *Am J Ophthalmol.* 2017;173:139–144.
2. Revere K, Davidson SL. Update on management of herpes keratitis in children. *Curr Opin Ophthalmol.* 2013;24:343–347.
3. White ML, Chodash J. Herpes simplex viral keratitis: a treatment guideline. *Compendium of Evidence-Based Eye Care.* 2014;1:1–76.
4. Liu S, Pavan-Langston D, Colby KA. Pediatric herpes simplex of the anterior segment: characteristics, treatment, and outcomes. *Ophthalmology.* 2012;119:2003–2008.
5. Serna-Ojeda JC, Ramirez-Miranda A, Navas A, et al. Herpes simplex virus disease of the anterior segment in children. *Cornea.* 2015;34:S68–S71.
6. Hsiao CH, Yeung L, Yeh LK, et al. Pediatric herpes simplex virus keratitis. *Cornea.* 2009;28:249–253.
7. Tsatsos M, MacGregor C, Athanasiadis I, et al. Herpes simplex virus Keratitis: an update of the pathogenesis and current treatment with oral and topical antiviral agents. *Clin Exp Ophthalmol.* 2016;44:824–837.
8. Schwartz GS, Holland EJ. Oral acyclovir for the management of herpes simplex virus keratitis in children. *Ophthalmology.* 2000;107:278–282.
9. Van Velzan M, van de Vijver DAMC, van Loenen FB, et al. Acyclovir prophylaxis predisposes to antiviral resistant recurrent herpetic keratitis. *J Inf Disease.* 2013;208:1359–1365.