A **CONTINUING MEDICAL EDUCATION** PUBLICATION

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TOPICS IN Ocular Antiinfectives

Overnight Contact Lens Wear and Microbial Keratitis: Two Views

Bruce H. Koffler, MD, and Helen K. Wu, MD

Overnight orthokeratology could cut myopia progression in some children by 50%. But is it safe?

Myopia is the most common ophthalmic condition in the world, affecting upwards of 40% of individuals in the US and 75% in Asia.[1] Myopia rates have been increasing among children and young adults in recent decades, possibly due in part to increasing time spent performing intensive near-vision tasks involving computers, tablets, and smart phones.[1]

Parents, especially those who are near-sighted themselves, are often highly motivated to lessen the burden of myopia in their children. Overnight orthokeratology (ortho-K) is a method for temporarily correcting myopia using specially designed rigid gas permeable (RGP) contact lenses worn only at night to reshape the corneal epithelium during sleep (Figure 1). On awakening, the patient can see without glasses or contact lenses, although the effect wears off in just a few days.

In recent years ortho-K has been shown to retard myopia progression in young children. The effect on myopia progression is thought to occur because ortho-K decreases peripheral hyperopic blur, which is believed to be an important factor in driving the axial elongation that leads to myopia.[2]

Ortho-K, which produces central flattening of the cornea, is one of the few available means of curtailing progression of myopia in the young (Figures 2 and 3). Since overnight ortho-K was introduced to the American market in 2002, advances in the technology—including highly gas permeable lens material, reverse geometry lens designs, and corneal topography for precision fitting—have contributed to its slowly rising popularity among eyecare providers and families.[3]

Controversy

However, not all eyecare providers are ready to embrace overnight ortho-K, especially in children. They say the benefits do not outweigh the risks, particularly the low but potentially sight-threatening risk of infectious keratitis. In the early and mid-2000s, multiple case reports of infectious keratitis associated with overnight ortho-K in children and teens in Asia—including several that resulted in permanent visual compromise—raised safety concerns

FIGURE 1 Typical curvature of ortho-K lens. *(Image courtesy of Dr. Bruce Koffler.)*

See INSIDE for:

Viral Chorioretinitis: Current Approaches to Diagnosis and Management

by Thomas Albini, MD

TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Evaluate orthokeratology as an option for the reduction of myopia progression in young patients.
2. Select antiviral therapy and formulate appropriate treatment plan for patients with acute retinal necrosis (ARN) or CMV retinitis.

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within the eyecare community that still echo today.[4]

In 2007, the Canadian Ophthalmological Society issued a policy statement against the use of overnight ortho-K in children, citing those reports.[5] The American Academy of Ophthalmology, in a review published in 2008, neither rejected nor accepted overnight ortho-K, but concluded that safety could not be ascertained with confidence based on available clinical data, and larger clinical trials were needed.[6]

Since then, neither an expanded body of research nor growing clinical experience have been able to dispel the controversy surrounding the appropriateness of overnight ortho-K for refractive correction and myopia control.

Given this controversy, *Topics in Ocular Antiinfectives* is offering two perspectives on overnight ortho-K and microbial keratitis (MK). The first is from Bruce Koffler, MD, who is founder and medical director of Koffler Vision Group and an associate professor of ophthalmology at the University of Kentucky College of Medicine, Lexington, KY. Dr. Koffler has offered Corneal Refractive Therapy (a form of ortho-K) to adult patients since 2002 and to children since 2007.

A second perspective is offered by Helen K. Wu, MD, assistant professor of ophthalmology at Tufts University School of Medicine and director of refractive surgery at New England Eye Center, Tufts Medical Center, Boston, MA. Her practice offers refractive correction via spectacles, daily and extended wear contact lenses, RGP lenses, and refractive surgery. Dr. Wu does not offer ortho-K.

The Benefits Justify the Risks

Bruce H. Koffler, MD

I was initially skeptical about contact lens wear in children; however my observations as an investigator in the Stabilizing Myopia by Accelerating Reshaping Technique (SMART) study changed my view.[7] Most of the children in the study—ages 8 through 14 years—adapted well to the technique. They were excited to wake up and be able to see well without correction, and the use of lenses during sleep was convenient and

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STATEMENT OF NEED

Ophthalmologists face numerous challenges in optimizing their competencies and clinical practices in the realm of preventing, diagnosing, and treating ocular infections and their sequelae; these challenges include:

- The widespread "off-label" use of topical ophthalmic antibiotics to prevent and treat serious and sight-threatening infections—given the reality that the most widely used topical antibiotics in ophthalmology have FDA approvals restricted to bacterial conjunctivitis.
- The escalating levels of multi-drug resistance in common ocular pathogens.[1]
- The emergence and increasing prevalence of once-atypical infections that may require diagnostic and treatment techniques relatively unfamiliar to comprehensive ophthalmologists.[2]
- The introduction of new and potentially more efficacious and/or safe ophthalmic antiinfectives.[3]
- The introduction of new and potentially more accurate diagnostic techniques for ophthalmic infections.[4]
- Widespread discussion over the efficacy and safety of novel or alternative delivery techniques and vehicles for prophylactic ophthalmic antibiotics (including but not limited to intracameral injection and topical mucoadhesives).[5,6]
- Increased understanding of the inflammatory damage caused by ocular infections and the best ways to prevent/alleviate inflammation without fueling the growth of pathogenic organisms.

Given the continually evolving challenges described above, *Topics in Ocular Antiinfectives* aims to help ophthalmologists update outdated competencies and narrow gaps between actual and optimal clinical practices. As an ongoing resource, this series will support evidence-based and rational antiinfective choices across a range of ophthalmic clinical situations.

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FACULTY AND DISCLOSURE STATEMENTS

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Thomas Albini, MD, is an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute in Miami, FL. Dr. Albini receives research support from Genentech and is a consultant for Allergan, Bausch + Lomb, and Eleven Biotherapeutics.

Bruce H. Koffler, MD, is founder and medical director of Koffler Vision Group and an associate professor of ophthalmology at the University of Kentucky College of Medicine, Lexington KY. He is a member of the speakers bureau for Paragon Vision Sciences.

Helen K. Wu, MD, is an assistant professor of ophthalmology at Tufts University School of Medicine and director of refractive surgery at New England Eye Center, Tufts University, Boston, MA. She states that in the past 12 months, she has not had a financial relationship with any commercial organization that produces, markets, re-sells, or distributes healthcare goods or services consumed by or used on patients.

DISCLAIMER Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and professional development. The information presented in this activity is not meant to serve as a guideline for patient care. Procedures, medications, and other courses of diagnosis and treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, applicable manufacturer's product information, and comparison with recommendations of other authorities.

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well tolerated.

There were no episodes of MK in the SMART trial, nor have there been any clinical cases associated with overnight ortho-K in my practice. Prior to delving deeper into the potential risks of overnight ortho-K, let me review its benefits.

Ortho-K Benefits

Two pilot studies—the Children's Overnight Orthokeratology Investigation and Longitudinal Orthokeratology Research in Children—initially demonstrated the safety and tolerability of overnight ortho-K, as well as its efficacy in slowing axial elongation in children.[8,9] SMART was the first multi-center study of significant size (N = 267) to evaluate the effectiveness

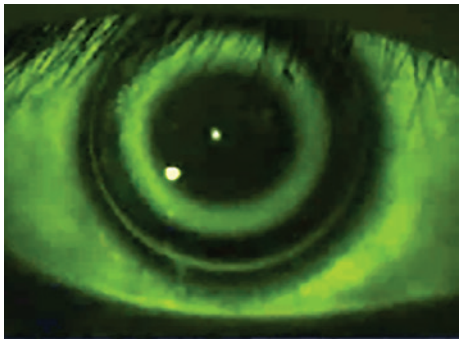

FIGURE 2 Fluorescein photo showing central flattening from ortho-K. *(Image courtesy of Dr. Bruce Koffler.)*

of overnight ortho-K in preventing myopia progression in children.[3] It demonstrated statistically significant retardation of myopia progression among children with mild to moderate myopia who underwent nightly overnight ortho-K compared with a control group who wore traditional silicone hydrogel soft contact lenses. The results of the SMART study are consistent with findings by other researchers. Kakita and colleagues in Japan demonstrated that, for the first 2 years of overnight ortho-K, axial elongation in myopic children aged 8 through 14 (n = 105) treated with overnight ortho-K was slower than among those whose vision was corrected with spectacles (0.15 mm vs 0.30 mm per year, respectively [$P < 0.0001$]). At 2 years, spherical equivalent refractive error among children treated with overnight ortho-K improved from –2.55 ± 1.82 D at baseline to –0.68 ± 1.02 D, while that of the control group progressed from –2.59 ± 1.66 to –3.83 ± 1.76 D, a relative difference of 3.1 D.[10]

In the study with the longest duration to date, the same group just mentioned continued their investigation of overnight ortho-K in a 59-patient subset.[11] They found that axial elongation was significantly retarded among overnight ortho-K wearers for the first 3 years, with the most marked reduction during the first year. At 5 years, refractive error among children in this subset treated with overnight ortho-K improved (from –1.89 ± 0.82 D at baseline to –0.70 ± 0.45 D), whereas spectacle corrected children progressed significantly (from –1.83 ± 1.06 D to –5.03 ± 1.83 D), a relative difference of 4.4 D. Overall, earlier treatment was associated with slower axial length elongation. There were no incidents of MK in overnight ortho-K treated patients over 5 years. Three cases of punctate keratopathy and one corneal erosion occurred in the overnight ortho-K group; all resolved after stopping lens wear for 1 week.[11]

In the 2-year Retardation of Myopia in Orthokeratology (ROMIO) study, Cho and colleagues reported a 43% overall retardation in axial elongation associated with overnight ortho-K wear.[12] They also noted that younger children had the greatest benefit.

Thus, cumulative evidence suggests the potential to cut refractive error by up to 50% using corneal reshaping, with the greatest benefit among children who initiate treatment young (roughly by age 7). Beyond vision improvement, preventing severe myopia may also be important for lowering risk for retinal detachment and other maculopathies later in life.

Safe Practices

Corneal reshaping practices vary considerably from country to country and continent to continent. In Asia,

CORE CONCEPTS

- There is evidence that overnight ortho-K slows axial elongation and reduces myopia progression, with the greatest effect on children aged about 7.
- Overnight wear of contact lenses is associated with a marked increase in rates of microbial keratitis; and there have been significant outbreaks of *Acanthamoeba* and *Pseudomonas* keratitis in children practicing overnight ortho-K.
- There remains insufficient data to determine unequivocally whether the likelihood of reducing a child's myopia outweighs the small risk of a devastating outcome.

where demand for ortho-K is very high due to the high prevalence of myopia, the training of eyecare providers fitting overnight ortho-K lenses was initially poorly regulated, and cases of MK emerged in the mid-2000s. Most if not all these cases were associated with significant breaches in hygiene, (eg, rinsing lenses with tap water). These countries have since tightened the regulatory protocol around overnight ortho-K, and the rates of MK have dropped dramatically.[2]

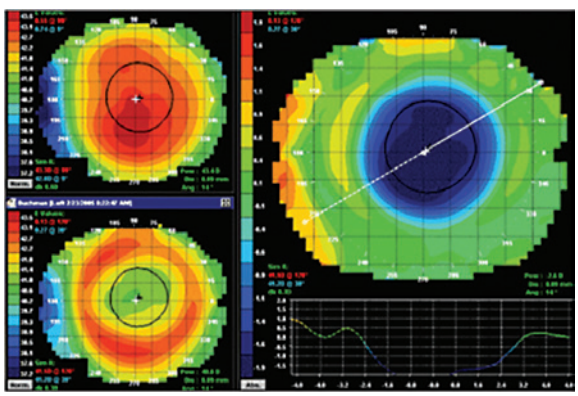

FIGURE 3 Pre- and post-ortho-K topography maps, with subtraction view, showing central flattening. *(Image courtesy of Dr. Bruce Koffler.)*

Currently in the US, practitioners must complete a certification course that

emphasizes the importance of compliance, cleanliness, and replacement of lenses. In my office, we involve the children and their caretakers, training them in insertion and removal and disinfection. We follow patients closely, including a first follow-up visit within 24 to 48 hours of initial placement. It is important to assess corneal staining at each visit and to instruct patients to come to the clinic immediately at the first signs of redness, pain, or new symptoms.

Microbial Keratitis

In compliance with an FDA mandate for post-marketing surveillance, and in conjunction with Ohio State University, two US ortho-K lens manufacturers conducted a retrospective assessment of MK incidence among patients using overnight ortho-K. Through chart review, researchers counted the number of red-eye related complications in 2005 and 2006 among 1317 patients prescribed overnight ortho-K from within 119 practices and found eight cases of corneal infiltrate associated with painful, red eye (six in children and two in adults). Two of the cases in children were classified as MK, but neither was associated with documented vision loss.[13]

These results suggest a rate of 7.7 cases of MK per 10,000 person-years of overnight ortho-K wear overall, and 13.9 cases per 10,000 person-years in children.[13] This is a low incidence, similar to or lower than the MK incidence associated with extended-wear silicone hydrogel lenses.[14]

The Risks Outweigh the Benefits

Helen K. Wu, MD

In the developed world, contact lens wear is the primary risk factor for the development of MK, contributing to over 10,000 cases yearly in the US.[15] Sleeping in contact lenses (whether appropriately or inappropriately) increases risk for MK above that associated with daytime wear by 10- to 15-fold, making overnight lens wear the greatest single risk factor for MK.[15]

Several factors may contribute to higher risk with nighttime lens wear: reduced corneal access to oxygen, absence of blinking, corneal surface microtrauma due to the presence of a contact lens, and the presence of opportunistic pathogens. In addition, overnight ortho-K lenses are designed to apply pressure to the corneal surface to flatten the epithelial layer by thinning it in the center and thickening it peripherally. Whether this epithelial thinning compromises the corneal barrier to microbial infection is not known.[2]

One of my main concerns with overnight ortho-K is hygiene. In my experience, lapses in contact lens hygiene are common among children and young adults; and I have seen these lapses result in serious sight-threatening infections. Failure to follow the cleaning/disinfection protocol contributed to many of the reported cases of MK associated with overnight ortho-K.[16] And while studies show that most children succeed at handling their lenses, we cannot predict which ones will occasionally err.[17]

MK Rates

In a review by Watt and Swarbrick, 123 cases of MK were reported in conjunction with overnight ortho-K use between 2001 and 2007, mostly in China and Taiwan, where overnight ortho-K is popular, but cases have also been reported in Israel, Europe, Australia, and the US.[16,18-25] While there are many unanswered questions about the causative factors in these cases and the manner in which lenses were prescribed, these reports remain alarming for several reasons.

First, most of these corneal ulcers occurred in children and teens. Second, many of the ulcers were central and severe.[4] Eighteen percent resulted in final best corrected visual acuity of 20/200 or worse.[16] Third, a majority of cases were caused by aggressive pathogens including *Pseudomonas* and *Acanthamoeba*.[16,18-20,22,23]

Animal studies suggest that *Pseudomonas* may be more adherent to ortho-K lenses compared with conventional RGP lenses.[26] A number of other pathogens have been associated with overnight ortho-K, including *Serratia marcescens*, *Xanthomonas maltophilia*, *Nocardia asteroides*, *Providencia stuartii*, *Burkholderia cepacia*, *Pseudomonas putida*, coagulase negative staphylococci, *Haemophilus influenzae* and *Corynebacterium spp*.[16,25] Lastly, infections occurred despite the use of advanced technology, including reverse geometry designs and highly oxygen permeable materials.[4]

It remains unclear whether better education of clinicians and patients and tighter regulatory control within the industry will prevent future outbreaks. One study in Taiwan showed increasing rates of pediatric MK in 2008-2012 compared to ten years prior in 1998-2002, which the authors correlated with increased overnight ortho-K use.[27]

With approval for overnight ortho-K already granted in the US (based largely on data from studies in adults), there is little chance of a prospective trial of sufficient size to provide reliable estimates of MK risk with overnight ortho-K in children.[4] This makes the available data—including case series and retrospective reviews currently in literature—all the more important. These indicate that the risk of significant injury, while small, is real.

Flawed Informed Consent

Children cannot give informed consent; they depend on adults to weigh the risks and benefits and make important medical decisions for them. Despite their best intentions, parents occasionally project their own desires (perhaps related to their own myopia) onto their children. Although rare, serious adverse events such as MK can turn from terrible to tragic when they occur in children, who may or may not have agreed to overnight ortho-K, if it had been up to them. Absent convincing clinical data in published trials and a consensus within the medical community, I do not currently recommend their use in children.[28]

Conclusion

There are things on which Drs. Wu and Koffler concur. These include limiting fitting of overnight ortho-K lenses

to providers who have fulfilled device-specific training requirements, taking time to counsel contact lens-wearing patients in detail about proper hygiene, lens and lens case handling disinfection, close follow-up and monitoring, and clear instructions to notify their provider immediately if there is eye redness or pain.

Evidence is emerging that myopia control with overnight ortho-K is possible. According to estimates based on retrospective post-marketing surveillance data, the risk of children developing MK from overnight ortho-K is low—approximately 14 cases for every 10,000 person-years of overnight ortho-K wear. However, MK associated with overnight lenses may be caused by very aggressive pathogens and lead to vision loss; hygiene lapses may contribute. Larger studies are needed for safety to be more firmly established.

Bruce H. Koffler, MD, is a member of the speakers bureau for Paragon Vision Sciences. Helen K. Wu, MD, states that in the past 12 months, she has not had a financial relationship with any commercial organization that produces, markets, re-sells, or distributes healthcare goods or services consumed by or used on patients. Medical writer Noelle Lake, MD, assisted in the preparation of this manuscript.

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Viral Chorioretinitis: Current Approaches to Diagnosis and Management

Thomas Albini, MD

The speed with which it progresses, and the serious harm it can do to patients' vision, make viral chorioretinitis a significant challenge for clinicians, but new diagnostic techniques and medications are changing the way this devastating condition is managed.

Viral chorioretinitis is a rare but sight-threatening condition caused by infection with viruses from the herpes family, including varicella zoster virus (VZV), herpes simplex virus (HSV), and cytomegalovirus (CMV). These viral infections typically present in one of two distinct forms: acute retinal necrosis (ARN) or CMV retinitis. While ARN commonly results from VZV or HSV in immunocompetent patients, CMV retinitis typically occurs as an opportunistic infection in immunodeficient patients such as individuals with advanced human immunodeficiency virus (HIV) infection.

Both ARN and CMV retinitis are characterized by necrotizing retinopathy in one or both eyes; in the absence of antiviral therapy this condition can progress rapidly and lead to substantial vision loss. To halt disease progression prompt recognition and initiation of aggressive treatment are of paramount importance. This presents a significant challenge to the managing clinician, as these are rare conditions with varying clinical presentations. In this article, we will review the clinical characteristics of viral chorioretinitis and discuss developments that have enabled clinicians to better recognize and manage these infections.

Acute Retinal Necrosis

The incidence of ARN was recently estimated at roughly one case per 2 million population per year.[1,2] It typically affects otherwise healthy individuals but may also occur in immunocompromised patients. Varicella zoster infection is the leading cause of ARN.[3] Other causes include infection with herpes simplex (type 1 or type 2), or, in rare instances, CMV or Epstein-Barr virus.[4]

Although ARN is relatively rare, for those affected by the condition the prognosis is usually poor. One reason why ARN can be so devastating is the frequency of secondary retinal detachment—more than half of ARN patients will develop retinal detachment, even with aggressive antiviral therapy.[5,6] This viral retinitis can also affect the optic nerve (papillitis), resulting in vision loss and sometimes herpetic encephalitis.

Furthermore, although the infection in ARN typically presents first in one eye only, it spreads to the contralateral eye in as many as one-third of patients.[7] The fellow eye involvement typically happens within 6 weeks but has been reported to occur even years after the initial presentation.[8]

CMV Retinitis

CMV retinitis classically affects AIDS patients and patients who are immunocompromised for other reasons (eg, cancer chemotherapy). CMV retinitis usually develops when CD4+ T-cell counts fall below 50 cells/mm^3, and it is the initial manifestation of HIV infection in many cases.

Before the introduction of "highly active antiretroviral therapy" (HAART), CMV retinitis accounted for the overwhelming majority of infectious retinitis cases in AIDS patients and over 90% of AIDS-associated blindness.[9,10] Although the advent of HAART has significantly reduced the incidence and complications of CMV retinitis, it remains the leading cause of vision loss in AIDS patients and is commonly seen in those who either have not received HAART or who have failed on HAART.

Similar to ARN, CMV retinitis is associated with a high rate of retinal detachment and poor prognosis. Studies have reported rates of retinal detachment as high as 70% in AIDS patients with CMV retinitis.[11]

TABLE 1

Standard Clinical Criteria for the Diagnosis of ARN *(adapted from Ref 12)*

- Focal well-demarcated areas of retinal necrosis located in the peripheral retina
- Rapid, circumferential progression of the necrosis
- Evidence of occlusive vasculopathy
- A prominent inflammatory reaction in the vitreous and anterior chambers

Clinical Diagnosis

Patients with ARN typically present with acute unilateral loss of vision, photophobia, and pain. Classic posterior-segment findings include severe intraocular inflammation, retinal vasculitis, and a yellow-white necrotizing retinitis. The retinitis usually begins in the periphery and progresses rapidly along axons toward the optic nerve. Often there is prominent inflammatory reaction in the anterior segment as well as in the vitreous (vitritis), which may make it difficult to visualize the retina. The American Uveitis Society in 1994 proposed diagnostic criteria for ARN based solely on clinical characteristics and progression of the disease (Table 1).[12]

CMV retinitis typically presents as a white hemorrhagic retinitis that emanates from the retinal blood vessels. The retinitis tends to progress more slowly than in ARN, and because of the immunocompromised state of the patients, inflammatory response is usually absent in the vitreous, allowing a clear view to the retina. Occasionally, patients will display frosted branch angiitis, a retinal vasculitis characterized by heavy perivascular exudates and sheathing, retinal edema, and retinal hemorrhages. Although not pathognomonic, the presence of frosted branch angiitis in association with retinitis points strongly to CMV infection.

The most important imaging modality in these patients is wide-field fundus photography, the purpose of which is to document—to the degree possible—the extent as well as the rate of progression of the retinal necrosis. Photos are typically taken each time the patient is seen, which may be as often as 2 or 3 times per week early on. For ARN patients who present with bilateral involvement, imaging of the brain may be helpful, since bilateral presentation implies the possibility of spread through the optic chiasm.

Laboratory Testing

Although ANR and CMV retinitis are usually diagnosed on the basis of clinical appearance, laboratory testing can be useful in atypical or challenging cases. Serum quantitative viral polymerase chain reaction (PCR) may be useful, particularly in transplant patients with a CMV viremia that may predispose them to CMV retinitis. Since these viral infections are usually associated with systemic antibodies, serological testing for HSV, VZV, or CMV antibodies can be helpful in supporting or excluding a specific viral infection.

Its speed and sensitivity make PCR another valuable tool in the diagnosis and management of viral retinitis. The sensitivity and specificity of the PCR analysis for viral DNA from an aqueous or vitreous tap are reported to be greater than 95% and 97%, respectively, for the diagnosis of VZV, HSV, and CMV.[13-15]

CORE CONCEPTS

- **Viral chorioretinitis manifests in two distinct forms of necrotizing retinopathy: ARN and CMV retinitis.**
- **ARN is caused by infection with VZV or HSV, typically in an immunocompetent host. Key features of ARN include severe anterior uveitis or vitritis, retinal vasculitis, and retinal necrosis.**
- **CMV retinitis affects immunocompromised patients and has been responsible for the majority of infectious retinitis in AIDS patients. The necrotizing retinitis is slowly progressive and is associated with minimal vitreous inflammatory response.**
- **Patients with ARN or CMV retinitis are at increased risk for developing secondary retinal detachment, which is a major contributor to ocular morbidity associated with viral chorioretinitis.**
- **The diagnosis of ARN and CMV retinitis is essentially clinical. PCR analysis of aqueous or vitreous samples may provide critical diagnostic clues in patients with atypical lesions or patients not responding to standard antiviral therapy.**
- **The treatment mainstay for viral chorioretinitis is systemic antiviral therapy. Intravitreal antiviral injection is primarily an adjunctive measure and may benefit those intolerant to or without immediate access to systemic therapy.**

While there is no doubt about the diagnostic efficacy of PCR, my clinic does not perform the test routinely, because in most cases ARN or CMV retinitis can be diagnosed without it. PCR is most useful when diagnostic challenge arises, and this happens most often in cases with a strong vitritis or vit-

reous hemorrhage precluding a fundus view or in cases with an atypical pattern of infection.

Systemic Antiviral Therapy

Because there is a high risk of spread to the fellow eye or the brain, systemic antiviral therapy has been the mainstay treatment for viral chorioretinitis. This treatment should be initiated immediately and aggressively, as patients can lose a substantial amount of vision even over the course of a day.

The traditional treatment for ARN has been the use of intravenous acyclovir at 10-15 mg/kg three times daily followed by oral acyclovir. Valacyclovir, an acyclovir prodrug, given at 1-2 gm three times daily has greater bioavailability than oral acyclovir and is able to achieve intraocular acyclovir levels comparable to those obtained with intravenous acyclovir.[16]

The current standard treatment for CMV retinitis is either intravenous ganciclovir or oral valganciclovir. The latter was found to be as effective as the intravenous treatment; it is also more convenient as it does not require hospitalization.[17] We typically give 900 mg of valganciclovir twice a day for the first 2 weeks, and then reduce the dose to 450 mg twice a day until the patient's CD4 count is 100 or greater on two consecutive readings.

In patients that are immunosuppressed for other reasons than AIDS it is difficult to know when to stop valganciclovir treatment. When making treatment plans, the clinician should take into consideration the fact that certain long-term side effects of valganciclovir—such as bone marrow suppression—need to be monitored.

When patients fail to improve on standard treatment, it is useful to reconsider the diagnosis. Infections with other non-viral agents including bacteria, fungi, and *Toxoplasma gondii* may present with retinitis that mimics ARN. Necrotizing retinitis can also occur from other conditions, such as Beçhets disease, sarcoidosis, lymphoma, or leukemia.

Intravitreal Antiviral Therapy

A combination of systemic and intravitreal antiviral therapy has emerged as a new treatment option for viral chorioretinitis. Intravitreal injection is believed to provide added efficacy by producing high concentrations of antiviral medication at the infection site. The principal intravitreal antiviral agents are ganciclovir (2 milligrams per 0.1 mL) or foscarnet (2.4 milligrams per 0.1 mL); either can be administered by injection through the pars plana into the vitreous cavity with a small gauge needle. Ganciclovir and foscarnet can also be combined. Injections may be repeated twice weekly, and severe cases may require 4 injections over two weeks.

Treating viral chorioretinitis with intravitreal agents alone is dangerous because it does little to prevent spread to the contralateral eye. ARN, in particular, may progress rapidly over 24 hours. For this reason intravitreal injection of an antiviral is considered adjunctive to the mandatory systemic antiviral therapy.

Indeed, many cases of viral retinitis require no local treatment at all. Intravitreal antiviral injection is most helpful for patients in whom the retinitis involves or threatens either the optic nerve or the macula. Local therapy also provides an alternative treatment for those intolerant to or without immediate access to systemic therapy.

Role of Corticosteroids

In ARN patients who are at risk of vision loss due to significant inflammation, such as moderate to severe vitritis or serous retinal detachment involving or threatening the macula, use of oral corticosteroids may be considered. Some clinicians believe that all patients should be given high doses of corticosteroids to block the inflammation. In any case, caution should be taken with corticosteroids as they can promote viral replication in the absence of antiviral therapy.

Use of an oral antiplatelet agent such as aspirin has been advocated as an adjunctive measure to prevent vascular occlusion, which may occur as a result of endothelial damage and inflammation in the retinal vessels in ARN, but the benefit of such treatment remains controversial.[18]

Managing Retinal Detachment

Retinal detachment occurs in a majority of patients affected by viral retinitis and represents a major risk factor for vision loss. It is typically rhegmatogenous, resulting from retinal holes in atrophic retina caused by the retinitis. These small retinal holes are often posterior and present in large numbers, making the detachments difficult to repair. In the case of ARN, there is sometimes a tractional component to retinal detachment as well because of intraocular inflammation.

The retinal detachments in these cases almost always require silicone oil to hold the retina in place following vitrectomy. During the surgery, intravitreal ganciclovir and/or foscarnet can be injected straight into the silicone oil after the retinal detachment repair is finished. The value of a scleral buckle is debatable, but it can be particularly helpful when there are retinal tears anterior to the equator.

Early vitrectomy with intravitreal acyclovir lavage has been reported to lower the risk of retinal detachment in ARN patients, but the benefit of prophylactic surgical intervention remains contentious.[19]

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 48

This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc. **DIRECTIONS:** Select the one best answer to each question in the Exam (Questions 1–10) and in the Evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. There is no fee to participate in this activity. *You can take the test online at* **http://cme.ufl.edu/ocular**.

1. Which of the following is not included in the diagnostic criteria for ARN defined by the American Uveitis Society?
   A. Rapid progression without antiviral therapy
   B. Positive PCR results from vitreous tap
   C. Peripheral necrotizing retinitis
   D. Prominent vitritis

2. The greatest slowing of axial elongation has been found in:
   A. Younger children (age approximately 7 years)
   B. Older children (age > 10 years)
   C. Age was not a factor in the effect on axial elongation
   D. Age was only a factor in specific ethnicities

3. Which of the following is NOT a typical finding in patients with ARN?
   A. Anterior chamber inflammation
   B. Retinal vasculitis
   C. Frosted branch angiitis
   D. Vitritis

4. Which of the following statements is/are true regarding myopia?
   A. Its prevalence in the US is approximately 13%
   B. Its prevalence in Asia is almost 24%
   C. Its prevalence is increasing in children
   D. All of the above are true

5. The most common cause of ARN is:
   A. VZV
   B. HSV
   C. CMV
   D. Epstein–Barr virus

6. To optimize safety, providers who offer ortho-K lenses should:
   A. Encourage thorough rinsing of lenses in tap water
   B. Discourage parental involvement in children's lens care
   C. Prescribe antibiotics for patients to have ready in case of redness
   D. Undergo device-specific training by the manufacturer

7. CMV retinitis usually occurs in AIDS patients with a CD4+ T-cell count lower than:
   A. 5 cell/mm^3
   B. 50 cells/mm^3
   C. 200 cells/mm^3
   D. 500 cells/mm^3

8. Which of the following is thought to underlie the slowing of myopia progression that ortho-K provides?
   A. Increased intraocular pressure
   B. Decreased hyperopic blur in the peripheral retina
   C. Central corneal epithelial flattening
   D. Increased central hyperopic blur

9. Which antiviral agents are used in the adjunctinve intravitreal therapy for viral chorioretinitis?
   A. Ganciclovir
   B. Foscarnet
   C. Combination of ganciclovir and foscarnet
   D. All of the above are correct

10. Which of the following were associated with overnight ortho-K use in studies conducted by Kakita, Harioka and coworkers?
    A. Slowing of axial elongation
    B. Increased refractive error
    C. Increased risk for Staphylococcal microbial keratitis
    D. Both B and C are correct

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 48

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ANSWERS:

1.	A	B	C	D	**6.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

11. Extent to which the activity met the identified
    Objective 1: 1 2 3 4 5
    Objective 2: 1 2 3 4 5
12. Rate the overall effectiveness of how the activity:
    Related to my practice: 1 2 3 4 5
    Will influence how I practice: 1 2 3 4 5
    Will help me improve patient care: 1 2 3 4 5
    Stimulated my intellectual curiosity: 1 2 3 4 5
    Overall quality of material: 1 2 3 4 5
    Overall met my expectations: 1 2 3 4 5
    Avoided commercial bias/influence: 1 2 3 4 5
13. Will the information presented cause you to make any changes in your practice? Yes No
14. If yes, please describe: _____
15. How committed are you to making these changes? 1 2 3 4 5
16. Are future activities on this topic important to you? Yes No

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records.

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