One in a million. Acute retinal necrosis (ARN) — although thankfully rare, with some population-based studies pegging its incidence on the order of one in 1 million — can be a devastating condition. The majority of patients are relatively young and appear immunocompetent and, therefore, unsuspecting of this sight-threatening and occasionally bilateral diagnosis. As such, prompt recognition and treatment of this devastating disorder is paramount to maximize clinical outcomes.

Unfortunately, since ARN is such an uncommon condition, retina specialists lack large, randomized, controlled trials to offer guidance on optimal management. Controversies persist on best choice of antiviral agent and route of administration as well as if and when to employ corticosteroids. There is debate on whether there is a role for prophylactic laser or even early prophylactic vitrectomy surgery to reduce the risk of retinal detachment.

These controversies are addressed by Alexa L. Li, MD, Jessica G. Shantha, MD, and Steven Yeh, MD, all from Emory University, with an evidence-based approach and discussion of the current literature. They provide a straightforward management algorithm for approaching acute retinal necrosis that astute clinicians can employ to combat this devastating condition.

**INTRODUCTION**

Acute retinal necrosis (ARN) is an uncommon viral uveitic syndrome characterized by a diffuse necrotizing retinitis that can lead to devastating visual consequences if not promptly diagnosed and treated. Due to its rarity, there is a lack of prospective, randomized, controlled clinical trials in the literature regarding optimal diagnostic and treatment regimens. Retrospective studies have guided current practices, yet recent advances in molecular diagnostics and combination systemic and intravitreal therapies suggest improved outcomes. This review summarizes the most recent developments in the challenging management of patients with ARN.

**DIAGNOSIS OF ACUTE RETINAL NECROSIS**

The diagnosis of ARN is classically made through clinical examination based on the following criteria defined by the Executive Committee of the American Uveitis Society in 1994: at least one area of peripheral retinal necrosis with circumferential spread, anterior chamber and vitreous inflammation, occlusive vasculopathy, and rapid disease progression in the absence of therapeutic intervention.

Maintaining a clinical suspicion for ARN is critical, and prompt treatment should be administered when the clinical exam is suggestive of ARN. Although laboratory data are not currently listed in the diagnostic criteria for ARN, testing with polymerase chain reaction (PCR) is now widely utilized, as numerous studies have reported PCR testing of viral DNA in aqueous and vitreous samples. Analysis of ocular fluid with PCR testing has heralded a sensitivity and specificity of greater than 90% in the detection of varicella zoster virus (VZV), herpes simplex virus (HSV), and cytomegalovirus (CMV).

Studies have reported PCR positivity for HSV or VZV DNA in 79% to 100% of cases with suspected ARN. Furthermore, viral diagnosis can aid in prognostic recommendations for guiding further treatment. Wong et al. reported a greater degree of visual loss in patients with ARN caused by VZV (0.4 logMAR) compared to those caused by HSV (0.04 logMAR; P = .014).
SYSTEMIC ANTIVIRAL TREATMENT

Historically, intravenous antiviral therapy was the standard of care in treating ARN. Blumenkranz et al. demonstrated regression of retinitis in 13 eyes with ARN treated with intravenous acyclovir 1,500 mg/m^2/ day, and Palay et al. reported a significant reduction in fellow eye involvement (P = .001) with treatment of intravenous acyclovir. However, the development of newer oral antiviral drugs has led to the debate of whether intravenous or oral therapy constitutes the best initial treatment. Tibbetts et al. compared 36 eyes treated in the intravenous acyclovir-only era (1981-1997), with 22 eyes treated in the newer antiviral era (1998-2008) in a retrospective, multicenter study and found that there was no significant difference in the final visual outcome or development of retinal detachment (RD) with initial intravenous or oral therapy. Similarly, Baltinas et al. performed a direct comparison between intravenous acyclovir and oral valacyclovir in 68 eyes with ARN and discovered that there was no difference in severe vision loss (P = .18) or RD rates (P = .67) across treatment groups. The results of these studies suggest that oral valacyclovir achieves comparable outcomes to intravenous acyclovir and can be utilized as the initial induction therapy for ARN, potentially reducing health care costs associated with inpatient treatment.

INTRAVITREAL ANTIVIRAL TREATMENT

Studies examining the role of adjunctive intravitreal antiviral therapy in combination with systemic treatment have also revealed promising results. A single-center, comparative, interventional case series of ARN patients investigated 15 eyes that received systemic treatment and 14 eyes that received combination systemic antiviral and intravitreal foscarnet injections (2.4 mg/0.1 mL). Patients receiving combination therapy demonstrated improved visual acuity (VA) by two lines or greater (P = .006), a decreased incidence of progression to severe visual loss (P = .02), and a reduced incidence of RD (P = .03). Similarly, Wong et al. reported a significantly lower risk of RD in 64 eyes with ARN receiving adjunctive intravitreal therapy compared to 40 eyes receiving systemic treatment alone (36% vs. 60%; P = .02). These studies suggest that combination intravitreal and systemic therapy may have favorable effects on visual and anatomic outcomes and should be considered for initial therapy in ARN patients. At our institution, suspected ARN patients typically receive oral valacyclovir 1,000 mg to 2,000 mg three times daily with combination serial foscarnet injections (2.4 mg/0.1 mL) every 3 days as induction therapy until disease quiescence is achieved, with maintenance treatment comprised of oral valacyclovir and intravitreal antiviral injections on an as needed basis (Figure 1).

ROLE OF PROPHYLACTIC LASER

Prophylactic laser retinopexy has been proposed to reduce the high incidence of RD in ARN patients. Lau et al. reported that there was a statistically significant difference in the incidence of RD (P = .04) between eyes that received prophylactic argon laser retinopexy (35.3%) and eyes that did not receive prophylactic laser.

Figure 1. Management algorithm of acute retinal necrosis.
(80%). However, it is important to note that laser retinopexy was not performed on eyes with a severe media opacity, and that the mean presenting VA was worse in the group that did not receive laser. This suggests the potential for bias toward deferring laser retinopexy in eyes with more severe vitreous inflammation that may confer a potentially higher risk of RD.

By contrast, Risseeuw et al. performed an analysis adjusting for severity of disease and did not find a risk reduction in the rate of rhegmatogenous RD (RRD) in ARN patients treated with prophylactic laser. Tibbetts et al. similarly found that prophylactic laser did not seem to affect the rate of RD, as RD occurred in 58% (11 of 19) of eyes treated with prophylactic laser versus 46% (18 of 39) that did not have laser treatment ($P = .40$). The decision to treat with prophylactic laser was made at the discretion of the treating physician in this study, making it difficult to directly compare the two groups. Selection bias inherently occurs when choosing patients suitable for laser prophylaxis, and future studies will need to adjust for this bias in order to distinguish the role of prophylactic laser in preventing RD in ARN patients.

**ROLE OF EARLY VITRECTOMY**

Several authors have promoted the role of early vitrectomy to prevent RD and improve visual outcomes. Hillenkamp et al. discovered that 90% of 20 eyes treated medically with intravenous acyclovir and oral prednisolone developed RD compared to 40% of 10 eyes treated surgically with early vitrectomy, intravitreal acyclovir lavage, and when feasible, laser demarcation to necrotic retina, scleral buckling, and gas or oil tamponade ($P = .007$). However, despite the difference in RD rates, the final visual outcomes were similar. Iwashashi-Shima et al. also investigated the role of early prophylactic vitrectomy in ARN patients and found that there was no significant difference ($P = .071$) in retinal attachment status between the group of eyes that underwent early vitrectomy (58%) and the observation group (75%). Risseeuw et al. similarly did not find a statistically significant association between prophylactic vitrectomy and reduction in the rate of RRD. Currently, there is insufficient evidence supporting the role for early vitrectomy to prevent RD and severe vision loss in ARN patients. However, close monitoring is recommended given the risk of multiple, necrotic retinal breaks, development of a posterior vitreous detachment with vitreous inflammation and contracture, and high risk of severe vision loss following RD.

**CORTICOSTEROID USE**

Corticosteroids can be used topically and orally to decrease the severe inflammatory response associated with ARN. Some retina specialists advocate the addition of oral corticosteroids 24 to 48 hours after initiating antiviral treatment. Local periorcular or intravitreal corticosteroid injection may be associated with severe, rapidly progressive ARN and caution is advised as it may potentiate rapid progression of retinitis (Figure 2). Weissman et al. reported a patient with suspected optic neuritis who received intravenous solumedrol and later developed bilateral central retinal artery occlusions associated with fulminant bilateral acute retinal necrosis and meningitis. Some uveitis specialists have advocated local corticosteroid in the setting of cystoid macular edema after resolution of active retinitis; however, the potential for retinitis recurrence should be considered.

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**Figure 2.** Photo of the right eye of a patient with rapid progression of acute retinal necrosis following intravitreal corticosteroid (A). She eventually developed a retinal detachment prompting vitrectomy, endolaser, and silicone oil instillation but developed significant fibrovascular proliferation (B).
Choudhury et al. described an intervention case series of four ARN patients treated with valacyclovir (2 g three times per day) and oral corticosteroids (1 kg/mg/day) started 24 to 48 hours after antiviral treatment. Due to persistent vitritis, intravitreal triamcinolone acetonide (4 mg/0.1 mL) was injected 1 to 2 weeks later, resulting in decreased vitritis and improved final VA of 20/40 in 75% of the patients. However, larger-scale studies have not demonstrated an improvement in visual or anatomic outcomes with the use of corticosteroids.\(^7,11\)

**CONCLUSION**

In summary, recent studies suggest that the optimal management of ARN involves prompt treatment with high-dose oral valacyclovir as induction therapy, combined with intravitreal antiviral therapy. PCR testing can be utilized to confirm suspected ARN, but treatment should not be delayed while awaiting viral confirmation, given the high risk of progression in the absence of treatment. The American Academy of Ophthalmology Ophthalmic Technology Assessment Committee published a report in 2017 affirming the above recommendations and found that the evidence regarding prophylactic laser retinopexy and early vitrectomy are not well-established at this time. In addition, although corticosteroid use may improve inflammatory metrics measures associated with ARN, caution is advisable, particularly with local injection corticosteroid because of the risk of rapid progression and vision loss. Further studies are needed related to long-term prophylaxis for ARN recurrence and treatment paradigms that may optimize visual and anatomic outcomes.

**REFERENCES**


Alexa L. Li, MD, can be reached at Department of Ophthalmology, Emory Eye Center, Emory University School of Medicine, Atlanta, GA; email: alexandria.li@emory.edu.

Howard F. Fine, MD, MHS, can be reached at Rutgers Robert Wood Johnson Medical School; New Jersey Retina, 10 Plum Street, Suite 600, New Brunswick, NJ 08901; email: hfine@njretina.com.

Jessica G. Shantha, MD, can be reached at Department of Ophthalmology, Emory Eye Center, Emory University School of Medicine, Atlanta, GA; email: jessica.gowramma.shantha@emory.edu.

Steven Yeh, MD, can be reached at Department of Ophthalmology, Emory University School of Medicine, 1365B Clifton Road NE, Atlanta, GA 30322; email: steven.yeh@emory.edu.

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