Diagnosis and Treatment of Acute Retinal Necrosis

Acute retinal necrosis (ARN) is a rare condition, with an annual incidence of approximately 0.63 cases per 1 million population. The most common causative agent is varicella-zoster virus (VZV), followed by herpes simplex viruses (HSV) 1 and 2. ARN can occur in individuals of all ages, but HSV-2 seems to be more common in younger groups and VZV in older patients. Women and men are equally affected.

How AUS defines ARN. The Executive Committee of the American Uveitis Society established the diagnostic criteria for ARN, which require the following features: 1) at least one focus of peripheral retinal necrosis with well-defined borders, 2) rapid circumferential progression when antiviral therapy is not instituted, 3) occlusive vasculopathy (with arteritis), and 4) prominent vitreous and anterior chamber inflammation.

Although ARN was formerly believed to affect only immunocompetent individuals, it is currently established that immune status should not be factored into the diagnosis of this disease.

Clinical Presentation
Most cases of ARN are unilateral, although up to 30% of patients develop bilateral ARN (or BARN), usually over the course of weeks, but sometimes even years later. Patients usually present with rapid onset of nonspecific symptoms such as pain, redness, light sensitivity, and decreased vision.

On examination, the classic findings are pronounced anterior chamber and vitreous inflammation, retinal vasculitis (usually arteritis), and multifocal, peripheral, confluent patches of deep retinal yellowish white infiltrates with well-defined margins (Fig. 1A). When present, retinal hemorrhages tend to be limited.

Over time, there is rapid and circumferential progression of the peripheral lesions toward the posterior pole, as well as development of retinal necrosis, with an associated increase in vitreous inflammation.

In its late phases, ARN is characterized by the presence of vitreous traction and retinal atrophy, which often lead to retinal detachment (RD).

Diagnosis
Differential diagnosis. The diagnosis of ARN, as defined by the American Uveitis Society criteria, remains clinical, so a thorough history and ophthalmological examination are crucial. However, other etiologies of retinitis and vasculitis can be difficult to distinguish from ARN based solely on clinical exam. These include syphilis, toxoplasmosis, tuberculosis, endogenous endophthalmitis, Behçet syndrome, other forms of pan-
Progressive outer retinal necrosis and cytomegalovirus (CMV) retinitis should also be considered, but these have a distinct clinical presentation; both are observed only in immunocompromised patients and have minimal to no vitritis. Additionally, CMV retinitis often presents with very prominent hemorrhages and periphlebitis predominantly in the posterior pole.

**Diagnostic testing.** Because of the possible challenges in establishing the diagnosis of ARN clinically, polymerase chain reaction (PCR) analysis of intraocular fluids is commonly utilized as an adjunctive tool. PCR testing can be done with small sample volumes, has high specificity, and can be extremely helpful in confirming the diagnosis of ARN and excluding other causes of retinitis. Both aqueous humor and vitreous samples can be used, but aqueous is usually preferred because it is considered less invasive and safer to obtain.

PCR sensitivity for herpesvirus ranges from 84% to 100% in aqueous samples, and 78% to 100% in vitreous samples. PCR analysis can be complemented by the calculation of the Goldmann-Witmer coefficient (GWC), which compares intraocular to serum antibodies. A GWC of 6 or more is positive for intraocular infection, while values of 1 to 5 are considered suspicious, and those of less than 1 are negative.

All patients with suspected ARN should be tested for HIV. Additional tests to help rule out other conditions include syphilis serologies; toxoplasma titers; lysozyme and angiotensin-converting enzyme and chest x-ray or chest computed tomography to exclude sarcoidosis; interferon-release assay for Mycobacterium tuberculosis; and blood and urine cultures and Gram stain if endogenous endophthalmitis is suspected.

In addition, if the cause remains unknown, vitreous or retinal biopsy for cytology, histology, molecular diagnostics, cytokine analysis, microbiological stains, and cultures should be performed to evaluate for vitreoretinal lymphoma or atypical infection.

**Complications**

The development of RD is a common complication of ARN (Fig. 1B). According to recent data, RD is seen in only 2% of eyes at presentation, but up to 47% of cases eventually develop one. Eyes with a greater extent of retinitis at the time of diagnosis are at greater risk of developing RD and having poorer visual outcomes.

Other complications of ARN include phthisis and ocular hypopyon, proliferative vitreoretinopathy, epiretinal membrane formation, macular edema, and optic atrophy.

**Treatment**

Treatment should be initiated as soon as the diagnosis is suspected, without waiting for laboratory results. Of note, current treatment recommendations are based on retrospective case series with small numbers of patients because of the rarity of this disease.

**Systemic antivirals.** Systemic antivirals are the standard of care for the treatment of ARN. They can induce regression of active retinitis and reduce the risk of fellow-eye involvement. For many years, intravenous acyclovir was the agent of choice. However, the development of oral valacyclovir, which has similar bioavailability, has caused a shift in clinical practice, and most ARN cases can now be managed with oral antivirals.

For most adults without significant medical comorbidities, current evidence supports induction therapy with oral valacyclovir 2,000 mg three or four times per day (i.e., a total of 6,000-8,000 mg daily) for seven to 10 days. Famiciclovir (500 mg every eight hours) or valganciclovir (900 mg twice per day) can be used as alternatives, the latter especially in cases where CMV retinitis is suspected.

Hospital admission and induction therapy with intravenous antivirals (acyclovir 10 mg/kg three times per day for five to 14 days followed by oral antivirals) are usually required only for patients with the following comorbidities: inability to tolerate oral formulations, definitive or suspected associated systemic involvement, immunosuppression, or interfering social issues.

After induction therapy, the standard practice is to maintain patients on long-term oral agents (usually with 1 g of valacyclovir daily) for at least six months.

**Intravitreal injection of antivirals.** As intravitreal agents can achieve immediate therapeutic levels, intravitreal foscarnet (2.4 mg/0.1 mL) is a well-accepted option to use in combination with systemic antivirals for ARN treatment. Intravitreal ganciclovir (2.0 mg/0.1 mL) is an alternative.

Data to support this practice, however, remain controversial. Despite some reports suggesting that the use of intravitreal antivirals was associated with better visual outcomes and lower rates of RD, a recent meta-analysis reported nonsignificant differences. It is important to note that intravitreal foscarnet or ganciclovir should always be administered in association with systemic antiviral agents.

**Corticosteroids.** Topical corticosteroids are usually used in patients with ARN to improve anterior segment inflammation. Oral corticosteroids (usually 0.5 mg/kg/day) can also be considered, but data to support their benefit is lacking. If used, oral corticosteroids always require concomitant antiviral medication and are typically started 24 to 48 hours after the antiviral therapy has been initiated.

**Proposed Prophylactic Procedures**

**Laser retinectomy.** Some clinicians have advocated the use of prophylactic laser therapy to prevent the occurrence of RD in ARN. However, several studies have failed to show beneficial outcomes with this strategy, and there are currently not enough data to support it.

If performed, laser should be applied to the normal retina, posterior to the area of active retinal involvement. This might be challenging in inflamed, painful eyes with ARN, which often dilate poorly and have very hazy media.

**Early pars plana vitrectomy.** Another approach that has been proposed to reduce the risk of RD in ARN is early pars plana vitrectomy (PPV). This is based on the rationale that these patients are at increased risk of developing
necrotic retinal breaks and retinal traction, and PPV can release areas of traction, allow for adequate laser application if desired, and reduce the inflammatory burden. However, some of the literature published to date has failed to show the benefit of this strategy. A recent meta-analysis reported an improved rate of RD (22% vs. 45% with no prophylactic procedure) in eyes that received early PPV, but the difference was not statistically significant (95% confidence intervals 6%-58% and 39%-52%, respectively).

In conclusion, current evidence does not support the use of early PPV to prevent RD in cases of ARN. Given that RD in these patients conveys a high likelihood of severe vision loss, close monitoring for this complication is recommended.

**Conclusion and Key Takeaways**

ARN is a rare but serious infectious condition caused by herpesvirus. ARN should be considered in eyes with prominent vitreous and anterior chamber inflammation and evidence of one or more peripheral areas of retinal necrosis and occlusive vasculopathy with arterial involvement. Even though the diagnosis of ARN is clinical, PCR analysis of intraocular fluids is commonly utilized as an adjunctive tool because of its high specificity and sensitivity.

When ARN is suspected, systemic antivirals should be initiated without waiting for laboratory test results. For most patients, oral valacyclovir is the treatment of choice for induction therapy, with intravenous antivirals generally reserved for select cases. Regardless of the method of administration used for induction therapy, it should be followed by long-term treatment with an oral antiviral. Although clinicians frequently elect to use adjunctive intravitreal foscarnet, evidence to support this practice is limited. Prophylactic laser retinopexy and early PPV have also been proposed to reduce the risk of RD, but the benefits of these procedures remain to be established.

**References**


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