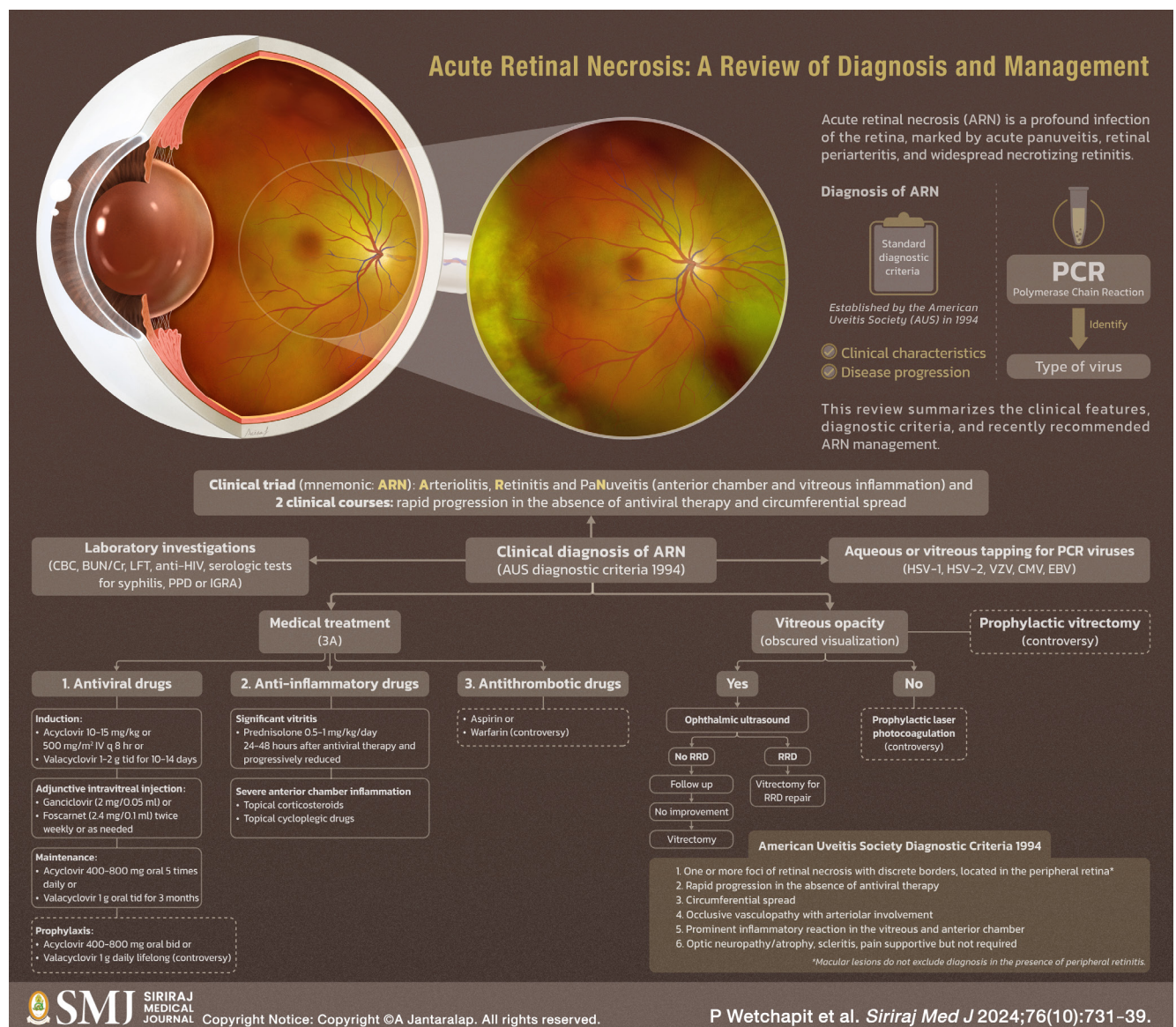


Acute Retinal Necrosis: A Review of Diagnosis and Management

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ABSTRACT

Acute retinal necrosis (ARN) is a profound infection of the retina, marked by acute panuveitis, retinal periarteritis, and widespread necrotizing retinitis. The etiology of ARN involves human herpesviruses, such as herpes simplex virus (HSV) and varicella-zoster virus (VZV), which can lead to severe visual impairment or even blindness. Diagnosis of ARN is based on clinical characteristics and disease progression according to the standard diagnostic criteria established by the American Uveitis Society (AUS) in 1994. The polymerase chain reaction (PCR) of aqueous specimens can enable identification of the type of virus. Early initiation of antiviral medication is essential for treatment efficacy to stop lesion progression, accelerate the healing process, and prevent contralateral eye involvement. Ocular complications of ARN include atrophic retina, multiple retinal breaks, rhegmatogenous retinal detachment (RRD), tractional retinal detachment (TRD), optic atrophy, macular edema, epiretinal membrane (ERM), and retinal and optic disc neovascularization. This review summarizes the clinical features, diagnostic criteria, and recently recommended ARN management.

Keywords: Acute retinal necrosis; necrotizing retinitis; panuveitis (Siriraj Med J 2024; 76: 731-739)

INTRODUCTION

Acute retinal necrosis (ARN) is an infrequent but severe retinal infection caused by human herpesviruses (HHV), which can result in significant visual impairment or even permanent blindness. In 1971, Urayama et al. provided the first account of ARN, reporting six patients with a clinical triad of unilateral acute panuveitis, retinal periarteritis, and diffuse necrotizing retinitis progressing to rhegmatogenous retinal detachment (RRD).¹ In 1977, Willerson et al. described two patients with bilateral acute retinal vaso-occlusive disease of an unknown etiology, in which the clinical courses were rapidly progressive necrotizing vasculitis and retinitis.² Young and Bird introduced the term “bilateral acute retinal necrosis (BARN)” in 1978 to describe a comparable condition identified in four patients.³ In 1982, Culbertson et al. discovered herpesviral particles in the retina of an enucleated eye, and varicella-zoster virus (VZV) was confirmed in two enucleated eyes and in the vitreous culture of one eye in 1986.^{4,5} Currently, the diagnosis of ARN is primarily based on clinical characteristics, with the presence of viruses in the intraocular fluid serving as confirmatory evidence.

This review summarizes the clinical features, diagnostic criteria, and recently recommended management of ARN based on current evidence so that ophthalmologists can confidently diagnose and provide timely treatment, which is essential for improving visual prognosis.

Epidemiology

The incidence of ARN worldwide is 0.50 to 0.63 cases per million population per year.⁶⁻⁸ In Thailand, the prevalence of ARN has been documented to vary between 0.2% and 3.9%.⁹⁻¹² ARN can affect both

immunocompetent or immunocompromised hosts without sex or race predilection.^{13,14} Accounting for 70% of cases, VZV emerges as the leading cause of ARN, succeeded by herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). Other rare causes of ARN are cytomegalovirus (CMV) and Epstein-Barr virus (EBV).^{4,5} The bimodal age distribution at the onset of the disease demonstrates peaks at approximately 20 and 50 years of age.¹⁵ VZV and HSV-1 ARN are more commonly found in patients older than 25 years old (mean age is 52 years old for VZV and 44 years old for HSV-1), whereas HSV-2 ARN is found predominantly in patients younger than 25 years old (mean age is 24 years old). This is due to the different ages of primary infection and reactivation of each herpes virus; specifically, HSV-2 is a reactivation of congenital infection, while VZV and HSV-1 are reactivations of the virus that were acquired during childhood or adulthood, but not perinatally.¹⁶⁻¹⁸

ARN can arise months to even years after primary infection or following cutaneous herpetic infection, such as chickenpox, shingle, herpes zoster ophthalmicus, or herpes genitalis. Concomitant herpetic keratitis and ARN can occur in approximately 20% of cases.¹⁹ HSV-1 and HSV-2 ARN have a tendency to be associated with previous, concurrent, or subsequent herpetic encephalitis and meningitis, respectively.^{16,17}

Clinical features

Most cases of ARN are unilateral diseases (65%–90%).^{7,20} However, in bilateral disease or BARN, the disease may begin unilaterally and may become bilateral in up to 35% of cases with and 70% of cases without antiviral therapy. The second eye can be affected as early as 6 weeks or up to years after the attack of the first eye.^{21,22}

ARN typically manifests as panuveitis, in which the symptoms include blurred vision, floaters, ocular pain, redness, and photophobia. The early course of the disease frequently exhibits anterior segment findings, including ciliary injection, keratic precipitates (small, stellate, large, or mutton fat KPs), anterior chamber cells and flares, posterior synechiae, and increased intraocular pressure. In the acute phase, posterior segment findings reveal vitritis, which represents an inflammatory response following cellular immunity to the virus. Multifocal patches of yellowish retinal infiltrates in the peripheral retina that progress circumferentially and posteriorly to confluent retinal necrosis are typical characteristics (Fig 1). Inflammation of the retinal vessels, predominantly arterioles or arteriolitis, is also a distinctive feature that can result in arteriolar occlusion and rapid retinal necrosis. Optic nerve involvement is typically characterized by disc hyperemia or swelling and a relative afferent pupillary defect. In addition, scleritis and episcleritis can occur.^{8,23} Patients with VZV ARN are more likely to have severe presentations than those with HSV ARN.^{6,8} In the late phase, fibrous membranes may develop on the retinal surface, causing the retina to contract, ultimately leading to retinal breaks at the junction of the normal and necrotic retina.²⁴⁻²⁷

Without treatment, retinitis tends to progress circumferentially by 360° in 5 to 10 days. Hence, dilated fundus examination is mandatory in every case before the diagnosis of anterior uveitis; otherwise, the diagnosis of ARN may be missed. Additionally, misleading treatment with systemic corticosteroids without antivirals can result in a severe rapid progression of retinitis and potentially devastating outcomes.

Diagnosis

Diagnosis of ARN relies on clinical features and disease progression, adhering to the standard diagnostic criteria established by the executive committee of the American Uveitis Society (AUS) in 1994.²⁸ In 2021, the Standardization of Uveitis Nomenclature working group established new classification criteria for research purposes.²⁹ Diagnostic criteria provide sensitivity while classification criteria provide specificity, which can support a low misclassification rate (Table 1). Table 2 presents the differential diagnoses of ARN.

Laboratory investigations

The key ancillary investigations for the diagnosis of ARN include the following.

1) Polymerase chain reaction (PCR) of aqueous or vitreous specimens. This method involves direct detection

of the viral genome by DNA amplification. It has an 82% sensitivity, 91% specificity, 96% positive predictive value, and 87% negative predictive value.³⁰ The use of PCR enables identification of the viral species, reduces the chance of misdiagnosis, and supports a proper initiation of induction with antiviral therapy.³¹ Aqueous tapping is easier to perform and safer with less complications than vitreous tapping. Aqueous sampling also offers a comparable yield for reporting positive PCR results with vitreous sampling.³²

2) Goldmann–Witmer coefficient (GWC). This test involves detecting local antibody production. It has an 81% sensitivity, 98.7% specificity, 97% positive predictive value, and 91% negative predictive value.³³ Specifically, the GWC compares specific antibody production between intraocular fluid and serum, which can be calculated using the following equation:

$$\text{GWC} = \frac{\text{intraocular fluid specific Immunoglobulin (Ig) G titer} / \text{serum specific IgG titer}}{\text{intraocular fluid total Ig} / \text{serum total Ig}}$$

Result interpretation

- 0.5–2 no specific intraocular antibody production
- 2–4 suggestive of specific intraocular antibody production
- ≥4 diagnostics of specific intraocular antibody production

3) IgG and IgM serology for herpes viruses. This test is not recommended for diagnosing ARN because it does not provide added value to the diagnostic process.

4) Endoretinal biopsy. This method is invasive and may be useful in cases in which the PCR result is negative but the clinical feature is highly suspicious or the cause of retinitis remains unknown.³⁴ The biopsy is performed at the demarcation line, especially in the acute phase of the disease, which increases the diagnostic yield.

5) Other methods include viral culture and immunocytochemistry from intraocular specimens, but these are generally limited by their poor sensitivity or specificity.^{4,5}

Baseline blood and serology testing

Baseline blood testing includes complete blood count, blood urea nitrogen, creatinine, and liver function test performed before the initiation of antiviral medication to allow adjusting the dose and monitoring drug toxicity in patients with renal impairment based on an induction dose and a maintenance dose recommendation. Serology testing is often needed to rule out other infectious agents that can affect the differential diagnosis of ARN (Table 2) and to assess the patient's immune status, including anti-HIV, syphilis, and tuberculosis testing.³¹

TABLE 1. Classification criteria for acute retinal necrosis.

Standardization of Uveitis Nomenclature (SUN) classification criteria 2021 ²⁹	
Criteria	
1.	Necrotizing retinitis involving the peripheral retina AND (either #2 OR #3)
2.	Evidence of infection with either HSV or VZV Positive PCR for either HSV or VZV from either an aqueous or vitreous specimen OR
3.	Characteristic clinical picture - Circumferential or confluent retinitis AND - Retinal vascular sheathing and/or occlusion AND - More than minimal vitritis^a
Exclusions	
1.	Positive serology for syphilis using a treponemal test
2.	Intraocular specimen PCR-positive for cytomegalovirus or <i>Toxoplasma gondii</i> (unless there is immunocompromise, morphologic evidence for >1 infection, the characteristic clinical picture of acute retinal necrosis, and the intraocular fluid specimen has a positive PCR for either HSV or VZV)

Abbreviations: HSV = herpes simplex virus; PCR = polymerase chain reaction; VZV = varicella-zoster virus.

^aVitritis criterion not required in immunocompromised patients.

TABLE 2. Differential diagnoses of acute retinal necrosis.

Infectious causes	Immune-mediated causes	Masquerade syndromes
Cytomegalovirus retinitis	Behçet's disease	Vitreoretinal lymphoma
Progressive outer retinal necrosis	Ocular sarcoidosis	Leukemia
Atypical toxoplasma retinochoroiditis		
Syphilitic chorioretinitis		
Fungal or bacterial endophthalmitis		
Ocular toxocariasis		

Treatment

Antiviral medications

Early initiation of antiviral medication is crucial for treating patients with ARN effectively. The goal of treatment is to stop lesion progression, accelerate the healing process, and prevent contralateral eye involvement. It was found in one study that treatment with systemic acyclovir decreased the risk of contralateral eye involvement from 70% to 13%.²² Table 3 summarizes the antiviral medications used in the treatment of acute retinal necrosis. The use of intravenous acyclovir for 10–14 days in the induction phase, followed by oral antiviral medication in the maintenance phase, is recommended as the standard initial treatment regimen. Regression of retinal lesions can be first seen 4–7 days after the initiation of treatment, and

complete regression can be observed at 6–12 weeks.^{23,35}

The duration of treatment for the maintenance phase with oral medication is recommended up to 6 weeks to 3 months to decrease the incidence of contralateral eye involvement. Low-dose oral antiviral therapy may be prescribed for long-term use as a prophylactic regimen; however, there is no consensus on the duration of this regimen. Adjunctive therapy with a twice-weekly antiviral intravitreal injection to provide immediate therapeutic vitreous drug levels for the early treatment of ARN is recommended until retinitis is controlled (Fig 2). There is evidence supporting the effectiveness of intravitreal antiviral therapy combined with systemic acyclovir in lowering the risk of severe visual loss and incidence of RRD in ARN cases.³⁶

Over the past several years, induction treatment with intravenous antiviral medications requiring hospitalization has shifted to the use of oral induction with newer antiviral medications that have been proven successful with greater bioavailability, including valacyclovir and famciclovir.^{31,37} Valacyclovir, an oral prodrug, metabolizes rapidly to acyclovir during first-pass metabolism, displaying a greater bioavailability of 54%–60% compared to oral acyclovir's lower bioavailability of 15%–30%. A dose of 1 g 3 times/day has a plasma level comparable to intravenous acyclovir of 5 mg/kg every 8 hours, and a dose of 2 g 4 times/day has plasma levels comparable to intravenous acyclovir 10 mg/kg every 8 hours. Famciclovir is an oral prodrug of penciclovir that has higher bioavailability (77%) than oral acyclovir. Penciclovir has a similar potency and antiviral spectrum to acyclovir and a favorable safety profile. This should be considered in patients with acyclovir-resistant ARN.

Anti-inflammatory drugs

Systemic corticosteroids, like prednisolone 0.5–1 mg/

kg/day with a tapering dose, may be initiated 24–48 hours after antiviral therapy to decrease the severe inflammatory response from vitritis, which can be significant and can limit visual acuity (VA). Topical corticosteroids are indicated in cases of anterior segment inflammation (>2+ cell grading or plasmoid aqueous formation) and posterior synechia formation.³⁸

Antithrombotic drugs

Aspirin and warfarin were used in one study in an attempt to prevent thrombotic complications.³⁵ Aspirin 81–650 mg/day may be considered in the acute stage with corticosteroids to prevent optic nerve and retinal ischemia.²⁴ However, no clinical trials have proven the efficacy of aspirin.³⁹

Prophylactic laser photocoagulation

The rationale for this is to prevent RRD. In this procedure, the laser is applied posterior to the demarcation line. Despite this, there is a lack of evidence suggesting

TABLE 3. Common antiviral medications used in the treatment of ARN^{31, 34}

Treatment	Induction 14 days	Maintenance 3 months	Efficacy	Side effects
Systemic treatment				
Acyclovir	10–15 mg/kg or 500 mg/m ² IV every 8 hours (1,500 mg/m ² /day)	VZV: 800 mg oral 5 times daily HSV: 400 mg oral 5 times daily	HSV-2 ~ HSV-1 > VZV >> CMV	Nephrotoxicity, neurotoxicity, malaise, diarrhea, nausea, vomiting
Valacyclovir	1–2 g 3 times daily	1 g 3 times daily	HSV-2 ~ HSV-1 > VZV >> CMV	Same as IV acyclovir
Famciclovir	500 mg 3 times daily	500 mg 3 times daily	HSV-1 > HSV-2 > VZV	Same as IV acyclovir
Intravenous Ganciclovir	5 mg/kg every 12 hours	5 mg/kg once daily	HSV-1 ~ CMV >> HSV-2, VZV	Thrombocytopenia, leukopenia, neutropenia, anemia, nephrotoxicity, diarrhea, nausea, vomiting, impairment of fertility, fetal toxicity and carcinogenesis based on animal data
Valganciclovir	900 mg twice daily	450 mg twice daily	HSV-1 ~ CMV >> HSV-2, VZV	Same as IV ganciclovir
Adjunctive intravitreal injection				
Ganciclovir	2 mg/0.05–0.1 ml twice weekly or as needed		HSV-1 ~ CMV >> HSV-2, VZV	Retinal detachment, vitreous hemorrhage, endophthalmitis
Foscarnet	2.4 mg/0.1 ml twice weekly or as needed		HSV-1 ~ HSV-2 ~ VZV > CMV	Same as IVT ganciclovir

CMV = cytomegalovirus; HSV-1 = herpes simplex virus type 1; HSV-2 = herpes simplex virus type 2; IV = intravenous; IVT = intravitreal; VZV = varicella-zoster virus.

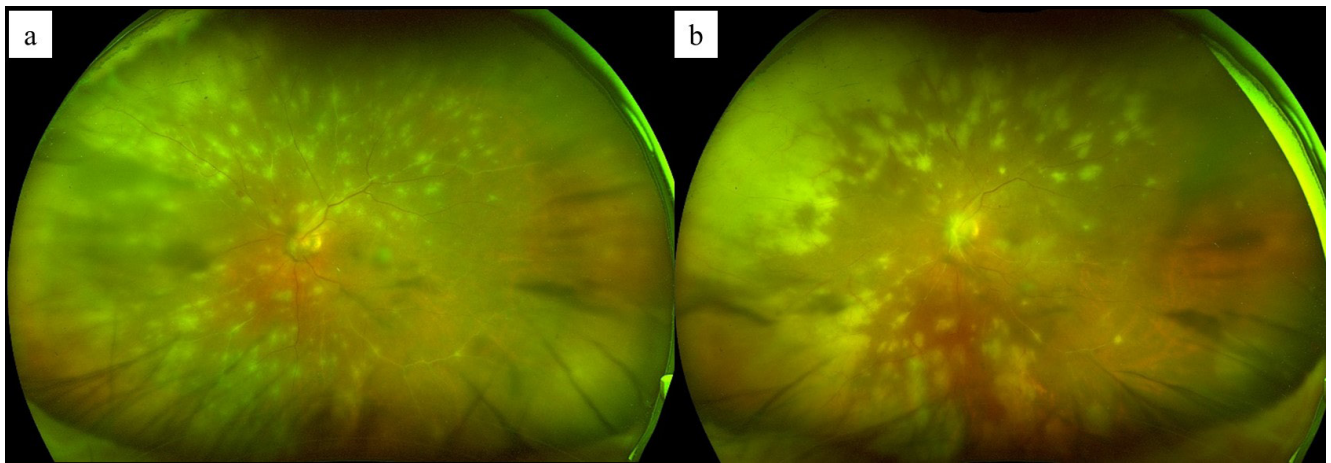


Fig. 1. Ultrawide-field fundus photograph of the left eye of an 80-year-old man with VZV ARN showing vitritis, occlusive arteriolitis, and multiple foci of retinal infiltrates with a discrete border at presentation (a). Two weeks later, the retinal infiltrates has become confluent and progressed circumferentially (b). ARN = Acute retinal necrosis; VZV = varicella-zoster virus

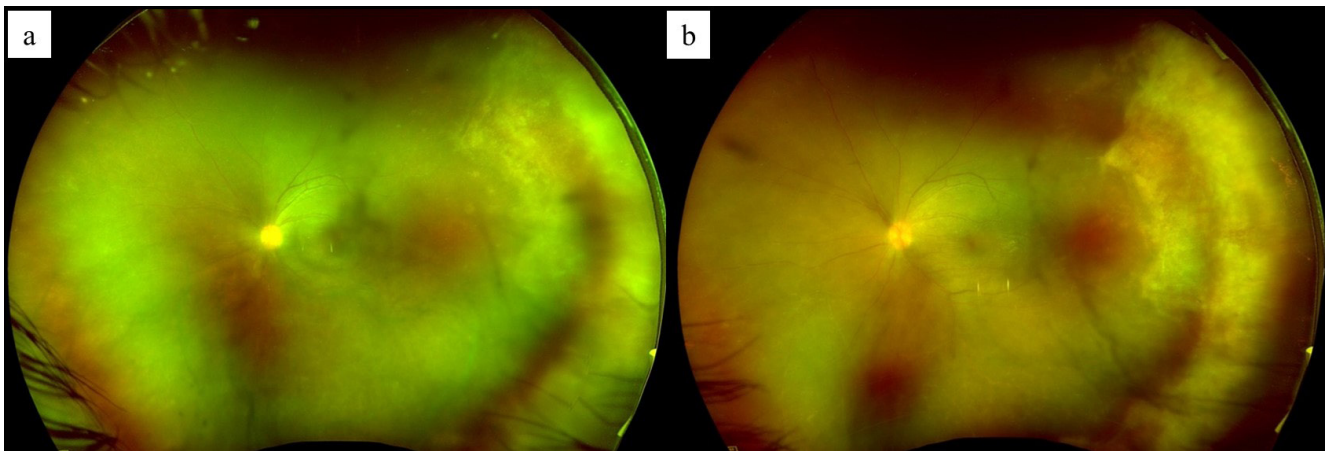


Fig. 2. Ultrawide-field fundus photograph of the left eye of a 13-year-old girl with HSV-2 ARN revealing vitritis, arteriolitis, and confluent retinitis in the temporal quadrant, with a partial response to acyclovir and IVT ganciclovir injections (a). Subsequent improvement in vitritis and retinitis was observed following adjunctive IVT foscarnet injections (b). ARN = Acute retinal necrosis; HSV-2 = herpes simplex virus type 2; IVT = Intravitreal.

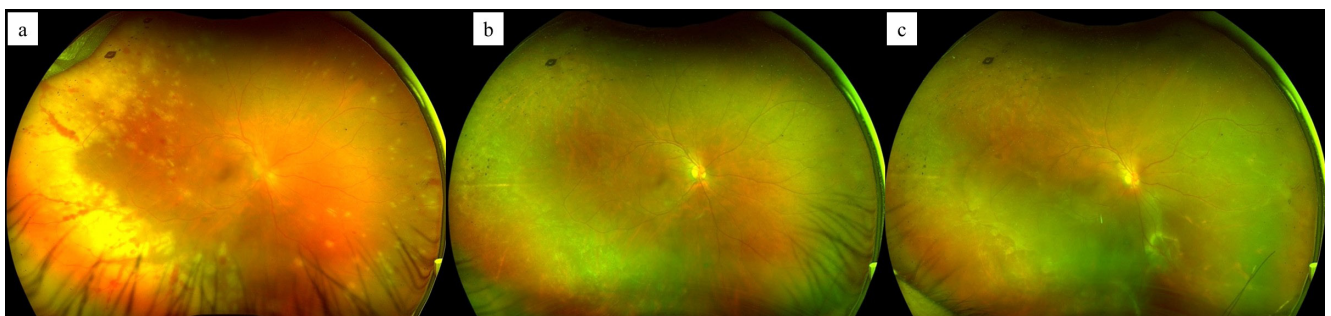


Fig. 3. Ultrawide-field fundus photograph of the right eye of a 48-year-old man with VZV ARN revealing occlusive vasculopathy and multiple foci of retinitis becoming confluent in the nasal quadrant (a). Resolution of ARN was observed after treatment with systemic acyclovir and IVT ganciclovir injections (b). Six months after the onset of ARN, RRD developed (c).

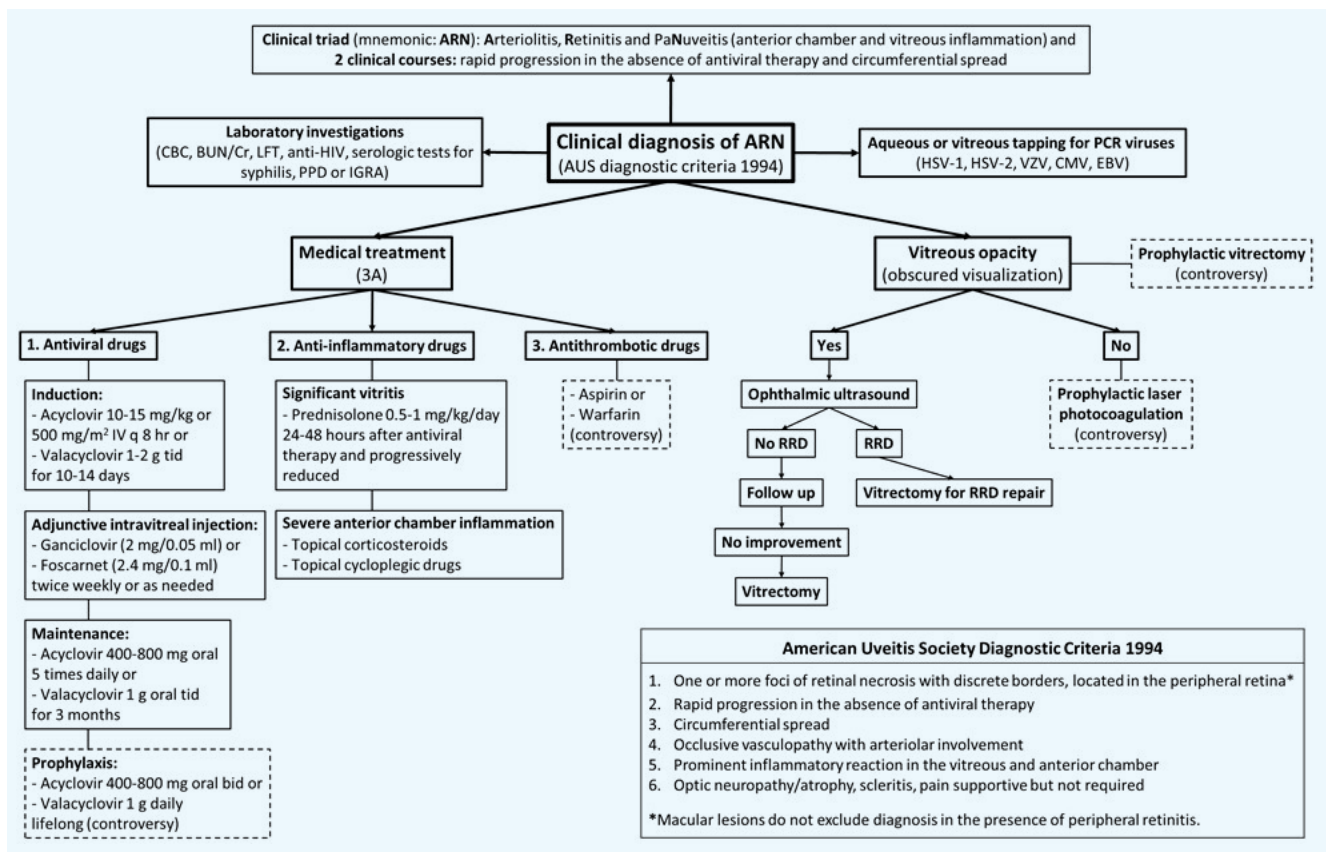


Fig. 4. Summarized diagnosis and management of acute retinal necrosis.

AUS = American uveitis society; BUN/Cr = blood urea nitrogen/creatinine; CBC = complete blood count; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; HSV-2 = herpes simplex virus type 2; IGRA = interferon-gamma release assay; IV = intravenous; LFT = liver function test; PPD = purified protein derivative; PCR = polymerase chain reaction; RRD = rhegmatogenous retinal detachment; VZV = varicella-zoster virus.

that prophylactic laser photocoagulation decreases the incidence of RRD due to limitations in the findings of various studies. Furthermore, laser photocoagulation can only be administered when there is adequate clarity of the ocular media to enable visualization during the procedure.³⁷

Vitreoretinal surgery

Vitrectomy for the surgical repair of RRD

Pars plana vitrectomy with endolaser photocoagulation and silicone oil tamponade is the most frequently applied technique for retinal detachment repair. Despite this surgical repair technique allowing good anatomic results, the visual outcome may be poor from optic and retinal atrophy.²⁴

Prophylactic vitrectomy

The rationale in this approach is the removal of inflammatory mediators and vitreous traction, applying laser demarcation of the necrotic retina, and placing a long-acting tamponade to prevent RRD. A retrospective

case series showed that early prophylactic vitrectomy with or without silicone oil reduced the incidence of RRD but did not change the visual outcome. These results suggested that retinal ischemia and optic atrophy rather than secondary RRD were the main causes of poor final visual outcomes.⁴⁰

Complications

In cases where patients do not receive treatment, inflammation naturally subsides within 2–3 months, resulting in a 360° peripherally atrophic retina and multiple retinal breaks. RRD is a frequent complication that can occur in 50%–75% of eyes within 1–3 months (Fig 3).⁴¹ Tractional retinal detachment may occur as a consequence of vitreoretinal traction caused by severe vitritis. Development of optic atrophy is a frequent consequence in patients with initial optic disc edema. Macular edema is often caused by severe vitritis or is accompanied by an epiretinal membrane. Retinal and optic disc neovascularization may develop in patients with extensive retinal ischemia.

Prognosis

The visual prognosis of ARN is poor, particularly in patients who are not treated immediately. Poor visual outcomes are related to large areas of retinitis involving the posterior pole or macula, the presence of a relative afferent pupillary defect at the time of diagnosis, retinal detachment, increased age, relative immunosuppression, and a larger area of RRD.^{42,43} Final VA is often limited by structural complications, including RRD, optic atrophy, macular edema, occlusive retinal vasculopathy, chronic vitritis, epiretinal membrane, macular hole, and macular ischemia. In one study, 48% of the involved eyes had a final VA < 6/60 at 6 months. Among ARN patients with retinal detachment, 60% of eyes ended up with VA < 6/60.⁸ However, treatment with acyclovir and prednisolone was associated with a final VA > 6/60 with 32% of VZV ARN and 67% of HSV ARN eyes having a final VA > 6/12.⁶

CONCLUSION

ARN, although rare, is a devastating disease that can lead to severe visual loss if not treated rapidly. When a patient presents with anterior segment inflammation, a dilated fundus examination should always be performed. Failure to do so may result in a misdiagnosis of ARN, and the administration of systemic corticosteroids alone can lead to severe and rapidly progressive ARN. We recommend that ophthalmologists should not wait until the fulfilling diagnostic criteria are met before starting treatment. If fundus examination reveals peripheral retinitis and/or a history of preceding cutaneous herpetic infection or HSV keratitis, ophthalmologists should immediately start induction treatment with antiviral medications with or without adjunctive intravitreal antiviral injection (Fig 4). Optimal treatment can effectively halt disease progression and prevent the involvement of the contralateral eye. PCR of an aqueous fluid specimen is useful for confirming the diagnosis of patients with suspected ARN; however, treatment should not be postponed while awaiting the PCR results owing to the nature of swift advancement of the disease in the absence of antiviral therapy. After induction treatment has been completed, oral maintenance should continue for approximately 3 months. Oral antiviral prophylaxis is still controversial and prophylactic laser photocoagulation or vitrectomy are currently inconclusive and require further study.

Conflicts of Interest

The authors confirm that we have no conflicts of interest to declare.

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