Curr Treat Options Neurol (2019) 21: 36
DOI 10.1007/s11940-019-0579-9

Neurologic Ophthalmology and Otology (R Shin and D Gold, Section Editors)

Treatment Strategies for Neuroretinitis: Current Options and Emerging Therapies

Aaron M. Fairbanks, MD[1]
Matthew R. Starr, MD[1]
John J. Chen, MD, PhD[1,2]
M. Tariq Bhatti, MD[1,2,*]

Address
[*,1]Department of Ophthalmology, Mayo Clinic, 200 First Street Southwest, Rochester, MN, 55905, USA
Email: Bhatti.Muhammad@mayo.edu
[2]Department of Neurology, Mayo Clinic, Rochester, MN, USA

Published online: 5 July 2019

This article is part of the Topical Collection on *Neurologic Ophthalmology and Otology*

Keywords Neuroretinitis · Bartonella · Disc edema · Macular star · Cat scratch optic neuropathy

Abstract

Purpose of review To explore and critically appraise the published data on the current and emerging treatment modalities for neuroretinitis.
Recent findings The optimum treatment strategy for neuroretinitis due to *Bartonella henselae* in immunocompetent individuals is not clear and a matter of debate. The role of systemic corticosteroids in infectious neuroretinitis and the optimum immunosuppressive regimen for use in recurrent idiopathic neuroretinitis also remains ill defined.
Summary There is no class 1 evidence to support a specific treatment strategy for neuroretinitis. For uncomplicated *B. henselae*–associated neuroretinitis in immunocompetent patients, initiation of antibiotic and corticosteroid therapy remains controversial. In patients with severe vision loss and/or moderate to severe systemic symptoms, a 4- to 6-week regimen of doxycycline or azithromycin with rifampin may provide some benefit. The routine use of systemic corticosteroids in infectious neuroretinitis is not recommended. Targeted antimicrobial agents should be instituted in cases of neuroretinitis due to specific infectious etiologies (e.g., syphilis, Lyme disease, tuberculosis). Azathioprine may be beneficial in cases of recurrent idiopathic neuroretinitis. There is a need for collaborative, multicenter prospective studies to provide definitive guidelines regarding the use of antibiotics and corticosteroids and to evaluate future therapies in infectious and recurrent idiopathic neuroretinitis.

Introduction

Neuroretinitis is clinically defined as the combination of optic disc edema with macular edema, typically in a star-like configuration, but does not connote a specific etiology [1••]. In 1916, Leber described a patient with unilateral vision loss with optic disc edema and radially oriented retinal exudates, which he termed stellate maculopathy [2]. However, in 1977, Gass coined the term neuroretinitis, based on the fluorescein angiography (FA) findings of the macular edema emanating from the optic disc, rather than the retina itself [3]. More recently, from an anatomical perspective, it has been shown that fluid flows directly from the disc surface into the outer plexiform layer (OPL), down through the external limiting membrane to collect beneath the neurosensory retina; ultimately departing a lipid-rich exudate in a star-like pattern due to the radial configuration of the OPL (Fig. 1) [4].

The exact pathophysiology behind the optic disc vascular permeability in neuroretinitis remains uncertain but is thought to be due to either direct invasion of infectious vectors or an autoimmune phenomenon [5]. The direct invasion hypothesis has garnered increasing traction because the most common cause of neuroretinitis is infectious, specifically due to the fastidious Gram-negative bacillus, *Bartonella henselae*, the causative agent of cat scratch disease (CSD) [1••, 6]. In cases of *B. henselae*–associated neuroretinitis, the mean age of presentation is 24.5 years with a female to male ratio of 1.8:1 with nearly 75% of patients experiencing systemic symptoms [1••, 6]. On exam, these patients often have decreased visual acuity and optic disc edema with or without macular exudates. A relative afferent pupillary defect and central or cecocentral visual field defect may be present. The disease is typically self-limited with spontaneous resolution and return of good visual function.

The etiology of neuroretinitis can be divided into three broad categories: infectious, inflammatory, and idiopathic [7]. In addition to *B. henselae*, a variety of bacterial, viral, and fungal causes of neuroretinitis have been identified including Rocky Mountain spotted fever [8], tuberculosis [9], salmonellosis [10], Lyme disease [11], toxoplasmosis [12], leptospirosis [13], toxocariasis [14], syphilis [7], varicella zoster [15], Epstein-Barr [16], herpes simplex [17], West Nile [18], Zika [19], chikungunya [20], and histoplasmosis [21].

A heterogeneous group of inflammatory diseases have also been associated with neuroretinitis such as sarcoidosis [22], polyarteritis nodosa [23], Takayasu's arteritis [24], systemic lupus erythematosus [25], Vogt-Koyanagi-Harada disease [26], and inflammatory bowel disease [27]. There have also been reports of neuroretinitis in patients with paraneoplastic syndrome [28] and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies [29•]. Cancer patients treated with immune checkpoint inhibitors have also been documented to develop neuroretinitis [30•, 31]. As the name implies, neuroretinitis is a prominent clinical feature of the rare entity, idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome [32].

Up to a half of cases have no identifiable cause and are termed idiopathic neuroretinitis [2]. In addition to the above potential causes of neuroretinitis, it is important to exclude mimickers of optic disc edema and macular exudates (Table 1).

While most cases of idiopathic neuroretinitis are monophasic with substantial visual recovery even without treatment, there is a small subset of patients with recurrent idiopathic neuroretinitis characterized by recurrent attacks and poor recovery [27, 33–35]. In these patients, the average age at presentation is 28 years with no gender predilection. Unlike infectious neuroretinitis, recurrent idiopathic neuroretinitis is not typically accompanied by systemic symptoms prior to the onset of visual symptoms [33, 35]. The majority of these patients experience sequential bilateral involvement with an average of 3.6 attacks with a three-year interval between episodes. Cecocentral, arcuate, and altitudinal visual field defects commonly occur. In stark difference to other forms of neuroretinitis, the visual deficit often persists after an attack and recurrent attacks have a cumulative effect on vision, portending a poorer visual prognosis. In the largest study evaluating this population, only 36% of patients had both 6/12 (20/40) vision or better and retained more than two-thirds of their visual field [35].

Diagnostic evaluation

Most patients with neuroretinitis present with painless unilateral vision loss but occasionally can have bilateral simultaneous or sequential involvement. Detailed medical history should include recent travel, animal exposure, skin changes, lymph node enlargement, and systemic symptoms. Queries should be targeted

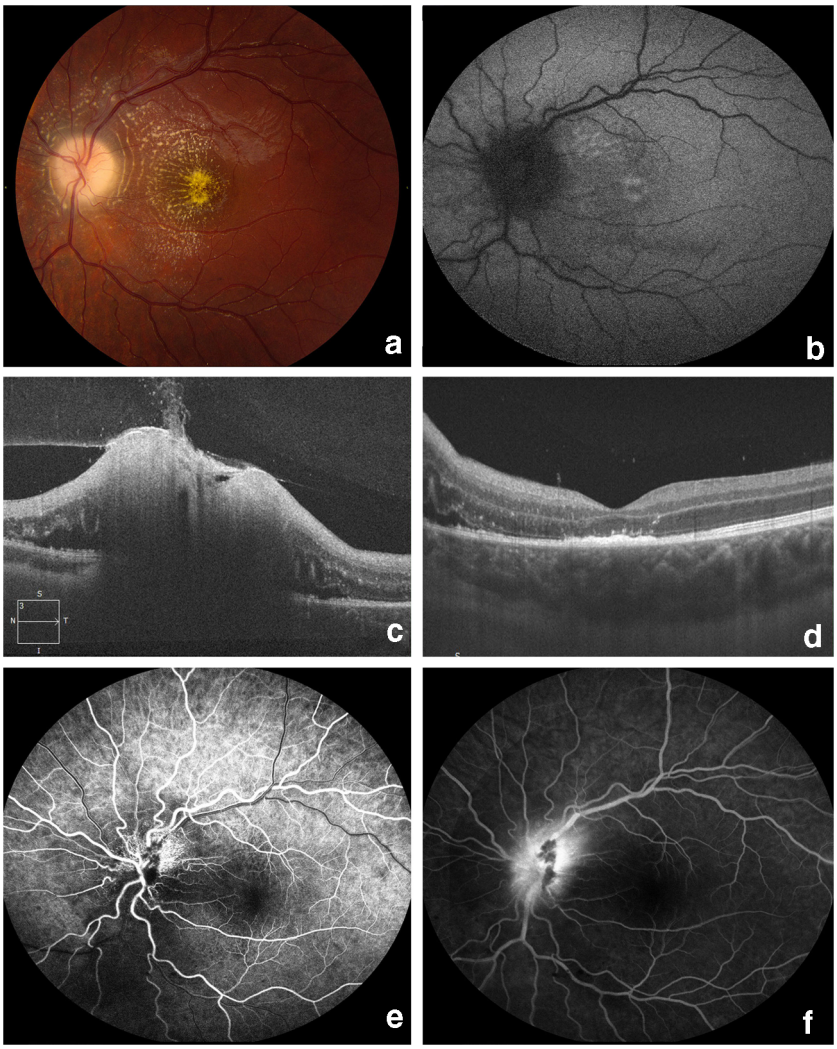

Fig. 1. Multimodality imaging of neuroretinitis: a14-year-old male with acute, painless, unilateral vision loss left eye. **a** Color fundus photography reveals diffuse optic disc edema with Patton's lines radiating around the optic disc with a stellate maculopathy and denser central exudates at the fovea. **b** Fundus autofluorescence with very faint circular hyperautofluorescence within the fovea corresponding to the denser foveal exudates. **c** Optical coherence tomography (Cirrus, Zeiss, Jena, Germany) of the optic nerve revealing massive disc edema with surrounding subretinal fluid and retinal thickening. **d** Optical coherence tomography (Cirrus, Zeiss, Jena, Germany) of the macula shows retinal thickening, blunted foveal contour, subretinal fluid extending from the optic disc, intraretinal hyperreflective material within the outer retinal layers, and subfoveally vitelliform deposits. **e** Early (15 s) fluorescein angiogram of the left eye demonstrates focal early hyperfluorescence of the superotemporal disc. **f** Late (5 min) fluorescein angiogram of the left eye shows diffuse disc edema with prominent leakage superotemporally.

Table 1. Differential diagnosis of optic disc with concomitant macular edema

Neuroretinitis
Arterial hypertension
Diabetic papillopathy
Papilledema
Anterior ischemic optic neuropathy
Posterior vitreous traction syndrome
Toxic (procarbazine and bischloroethylnitrosurea)
Juxtapapillary tumors/compressive lesions

toward identifying an underlying vascular disorder such as diabetes mellitus or arterial hypertension and autoimmune conditions. Aside from a complete neuroophthalmic examination, multimodality testing may be needed such as FA, fundus autofluorescence (FAF), optical coherence tomography (OCT), and fundus photography (Fig. 1). During the early phase, the classic macular star may not be present making the diagnosis challenging on fundoscopy alone. The macular fluid is often present for several weeks, before the visible radial exudates (i.e., macular star) form in the OPL [1••]. OCT can infer the diagnosis during this early stage of the disease process by identifying retinal thickening, flattening of the foveal contour, intraretinal fluid within the OPL and/or subretinal fluid, and early intraretinal hyperreflective exudates [36–38]. OCT is also useful in identifying peripapillary neurosensory retinal detachments in cases that never develop a macular star [36]. FA will reveal diffuse or segmental disc leakage, sometimes associated with leaking from a specific optic disc vessel [4]. Finally, FAF may reveal hyperautofluorescent macular exudates [39].

Neuroimaging is not routinely needed in the evaluation of neuroretinitis, but if done, it is preferable to obtain a dedicated orbital magnetic resonance imaging (MRI) study with fat suppression and contrast administration to rule out a retrobulbar optic neuritis. Optic neuritis due to multiple sclerosis (MS) can mimic neuroretinitis [40]; however, true neuroretinitis is not associated with MS [41]. Williams et al. postulated an association between MS and neuroretinitis; however, all of the patients with so-called neuroretinitis had an atypical fundus appearance and had been treated with interferon beta, which may have led to increased optic disc vascular permeability [40]. In some cases of neuroretinitis, the MRI may show enhancement of the intraocular portion of the optic nerve (i.e., optic disc) or extend slightly posteriorly behind the globe, but not to the same extent as seen with retrobulbar optic neuritis [42, 43]. Some experts have argued that this retrobulbar short segment enhancement is specific for *B. henselae*–associated neuroretinitis [43], but in other studies, no discernible differences could be made in differentiating the various etiological subtypes of neuroretinitis [27].

Laboratory testing should be performed depending on the zoonotic exposure history, systemic manifestations, and examination findings. As mentioned above, because CSD is the most common cause of neuroretinitis, *B. henselae* titers should be obtained in all cases, even if there is no patient recall of kitten exposure [1••,

44, 45•, 46, 47] and can be repeated after 4 to 6 weeks if the initial titers are negative and the clinical suspicion remains high [48]. Purified protein derivative or QuantiFERON-TB Gold testing should be obtained for patients with high risk tuberculosis exposure. For those with tick exposure or residing in endemic areas, testing for Lyme disease and Rocky Mountain spotted fever is recommended. Patients suspected of having sarcoidosis should undergo serum angiotensin converting enzyme levels as well as chest imaging (X-ray or computed tomography). Those with an exposure history to sexually transmitted diseases require testing for syphilis and the human immunodeficiency virus. Patients from endemic areas, particularly from the Ohio River Valley, should have histoplasmosis serology [49].

Management

The treatment of neuroretinitis is contingent upon the underlying etiology. As mentioned previously, a plethora of infectious and inflammatory conditions can result in neuroretinitis. Therefore, a careful diagnostic evaluation must be undertaken with the goal of initiating targeted therapy against the offending agent or process.

Infectious neuroretinitis

The following section will provide treatment recommendations for infectious neuroretinitis, with a special emphasis on CSD. It should be noted that all the available treatment data to date is from case reports, case series, and retrospective reviews. The lack of randomized trials upon which to make clear and firm clinical recommendations is an overarching theme that underscores the need for continued research and a collaborative multicenter approach.

Antibiotic therapy

Given the relatively benign natural history, there is debate whether to treat an episode of *B. henselae*–associated neuroretinitis. Several studies have examined the effect of antibiotics, corticosteroids, or a combination of both with conflicting results. In the only double-blind, randomized, placebo-controlled trial evaluating the use of azithromycin in patients with CSD, but without neuroretinitis, there was an 80% reduction in total lymph node volume in 50% of treated patients compared to only 7% in the placebo group [50]. Notably, there was no difference in any other clinical outcome measure. A retrospective review of 268 patients with CSD without neuroretinitis determined that the mean duration of lymphadenopathy was reduced in patients with moderate to severe systemic disease who were treated with effective antibiotics compared to those who were ineffectively treated or untreated [51]. The effective antibiotics included rifampin, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole, all of which have an intracellular action of inhibiting bacterial DNA or protein synthesis. *B. henselae* has a predilection for infecting endothelial cells and erythrocytes that sequesters it from antibiotics that primarily act against the bacterial cell wall (Appendix) [52].

Regarding antibiotic therapy in CSD with ocular involvement, two small case series demonstrated decreased disease duration and hastened visual recovery after treatment with doxycycline and rifampin (seven patients) [47] and marked

improvement in vision with ciprofloxacin with or without prednisone or doxycycline alone (four patients) [53]. A retrospective case series of 37 eyes of 24 patients with intraocular manifestations of CSD (six patients with neuroretinitis) demonstrated a vision of 20/200 or better in 86.5% of eyes who received a variety of different antibiotic therapies [54]. This perceived benefit is difficult to interpret because there was no control group for comparison. A more recent multicenter retrospective cohort study of 86 patients found a worse visual outcome in patients who received antibiotics alone compared to the combination of antibiotics and corticosteroids (see systemic corticosteroids and immunosuppressive medications section) [45•].

Immunocompromised patients infected with *Bartonella* species, including those with acquired immunodeficiency syndrome (AIDS), tend to experience worse systemic and visual complications and should be treated with antibiotic therapy [55, 56]. The use of a particular antimicrobial agent(s) depends on the specific clinical manifestation (endocarditis, bacillary angiomatosis, peliosis hepatis, bacteremia, etc.), but effective therapies include doxycycline, rifampin, azithromycin, erythromycin, and gentamicin. The recommended regimen for central nervous system involvement is a combination of doxycycline and rifampin [57].

In comparison, CSD in immunocompetent patients has been shown to be a self-limited disease process with excellent systemic and visual prognosis without treatment [56, 58]. In a retrospective case series of 24 patients with ocular *Bartonella* infection, final visual acuity was 20/25 or better in 74% of the patients and there was no difference in visual outcome between those who received antibiotic therapy (13 patients), with or without steroids, compared to those that were untreated [59]. A large, multicenter, retrospective chart review of 53 patients with CSD optic neuropathy found 68% of patients had a final visual acuity of 20/40 or better. Patients who presented with good (20/40 or better) visual acuity and those without systemic symptoms had better visual outcomes. However, there was no association between improved final visual outcome and antibiotic therapy [60]. The Centers for Disease Control and Prevention (CDC) acknowledges that most cases of CSD resolve without treatment, and the routine use of antibiotics in uncomplicated cases has not been established [61].

In addition to CSD, the treatments of other infectious causes of neuroretinitis have been evaluated, including Lyme disease, syphilis, and *Mycobacterium tuberculosis* (MTB). A case of Lyme associated neuroretinitis had initial worsening of vision after empiric initiation of oral prednisone (40 mg daily) followed by significant improvement once on oral doxycycline [11]. In another case of *Borrelia* associated neuroretinitis, the vision improved after a three-week course of ceftriaxone alone [62]. Both of these case reports suggest that antimicrobial therapy is needed prior to, or in concert with, the initiation of corticosteroid treatment in the setting of Lyme disease. In the broader literature examining the treatment of Lyme disease, there is a lack of consensus about the preferred treatment for neuroretinitis and the CDC defers to the primary literature to provide recommendations for the treatment of neuroborreliosis. Current guidelines recommend a 10- to 28-day course of oral doxycycline for ambulatory patients with early disseminated disease or acute neurologic Lyme disease. This includes patients with meningitis, cranial neuropathy (e.g., facial nerve palsy), and sensory or motor radiculopathy. However, intravenous ceftriaxone for 14 to 28 days is recommended for patients with more severe neuroborreliosis (e.g., encephalitis)

[63–65]. Where neuroretinitis falls on the spectrum of mild to severe neuroborreliosis has not been well defined. Furthermore, a European study demonstrated equivocal efficacy of a 14-day course of oral doxycycline compared to intravenous ceftriaxone in patients with neuroborreliosis [66]. Accordingly, in ambulatory patients with mild to moderate vision loss, but without evidence of other severe neurologic impairment from Lyme disease, we recommend treatment with oral doxycycline. In patients with evidence of more significant vision loss or neurologic disease, and who are more likely to be hospitalized, we recommend the use of intravenous ceftriaxone. Regarding syphilitic neuroretinitis, according to the CDC, aqueous crystalline penicillin G is the recommended treatment regimen for cases of ocular syphilis [67–70]. Limited evidence suggests ceftriaxone might be an effective alternative in penicillin allergic patients [67]. Patients for whom MTB is the suspected etiology of neuroretinitis should be treated in a similar manner to pulmonary disease. The CDC, American Thoracic Society, and the Infectious Diseases Society of America recommend the use of quadruple therapy (rifampin, isoniazid, pyrazinamide, and ethambutol) for two months followed by a four to seven-month continuation phase typically consisting of rifampin and isoniazid [71–73].

In summary, for *B. henselae*–associated neuroretinitis, there is no class I evidence to provide firm guidelines regarding the use of antibiotics. However, based upon the available data, working in concert with an infectious disease specialist, empiric treatment with doxycycline or azithromycin in addition to rifampin is appropriate for patients that are immunocompromised and patients that are immunocompetent with moderate to severe systemic symptoms or significant vision loss (Table 2). For those patients endorsing an allergic reaction to these medications, ciprofloxacin or trimethoprim-sulfamethoxazole may be substituted. For immunocompetent patients with mild to moderate vision loss without significant systemic symptoms, the decision to start antibiotic therapy becomes a nuanced discussion between the clinician and patient. One consideration is to treat empirically until an alternate infectious etiology has been excluded thereby allowing for either discontinuation or change in therapy. In terms of broad coverage, it is the opinion of the authors that doxycycline with rifampin for four to six weeks is appropriate because it not only covers CSD, Lyme disease, Rocky Mountain spotted fever, Weil's disease (leptospirosis), and with possible benefit against syphilis but also is generally well tolerated with good penetration into the central nervous system [47, 64, 67, 74, 75]. If an alternate infectious etiology is found, treatment should be tailored accordingly.

Pediatric consideration

For children less than eight years old, azithromycin and rifampin are the preferred choices. Traditionally, doxycycline has been avoided in children due to the possibility of tooth discoloration and enamel hypoplasia. However, a recent study supported by the CDC found no visible dental staining in children treated with doxycycline at an average dose of 2.3 mg/kg, average duration of seven days, and average of 1.8 courses per child for Rocky Mountain spotted fever [76].

Systemic corticosteroids and immunosuppressive medications

As with antibiotic therapy, there are no randomized, controlled clinical trials that have examined the role of systemic corticosteroids in *B. henselae*–associated

Table 2. Recommended antibiotic regimens for *Bartonella henselae*–associated neuroretinitis, neuroborreliosis, neurosyphilis, and intraocular *Mycobacterium tuberculosis*

	Medication	Recommended dose Adults	Children	Duration	Side effects	Comments
Bartonella henselae–associated neuroretinitis	Doxycycline	100 mg twice daily	≥ 45 kg = Adult dosing < 45 kg = 2.2 mg/kg twice daily	4–6 weeks	Photosensitivity Dental staining Intracranial hypertension Hypersensitivity reaction Esophagitis Hepatotoxicity	Avoid in pregnancy. Avoid in children < 8 years old**
	Rifampin	300 mg twice daily	10 mg/kg twice daily	4–6 weeks	Red/orange discoloration of body fluids Agranulocytosis DIC Hepatotoxicity Hypersensitivity reaction	Avoid in patients with HIV/AIDS on antiretroviral therapy—drug-drug interactions.
	Azithromycin	500 mg × 1 day, then 250 mg daily	> 45.5 kg = Adult dosing ≤ 45.5 kg = 10 mg/kg × 1 day, then 5 mg/kg daily	4–6 weeks	QT prolongation/Torsades de Pointes Transaminase elevation and hepatotoxicity Nausea/vomiting/diarrhea Myasthenic crisis Stevens-Johnson syndrome	Avoid in patients with a long QT interval and history of significant hepatic disease
	Ciprofloxacin	500 mg twice daily	10–20 mg/kg/dose twice daily	4–6 weeks	Arthropathy, tendon rupture Diarrhea CNS effects Peripheral neuropathy Myasthenic crisis QT prolongation	Avoid in children and the elderly
	Trimethoprim-sulfamethoxazole	160 mg (trimethoprim) twice daily	4 mg/kg (trimethoprim) twice daily	4–6 weeks	Nausea/vomiting Rash/allergy (sulfonamides) Inaccurate serum creatinine testing Folate deficiency Megaloblastic anemia Stevens-Johnson syndrome	Avoid in patients with sulfonamide allergy, HIV, pregnancy, children < 2 months old
Lyme disease	Doxycycline	100 mg twice daily	≥ 45 kg = Adult dosing < 45 kg = 2.2 mg/kg twice daily**	10–28 days	Photosensitivity Dental staining Intracranial hypertension Hypersensitivity reaction Esophagitis Hepatotoxicity	May be used in early neurologic Lyme disease in ambulatory patients. Used to treat neuroborreliosis in Europe.

Table 2. (Continued)

	Medication	Recommended dose Adults	Children	Duration	Side effects	Comments
	Ceftriaxone (IV)	2 g daily	75–100 mg/kg/day	14–28 days	Diarrhea, *Clostridium difficile colitis* Biliary stasis ceftriaxone-calcium salt precipitate within the gallbladder (pseudolithiasis)	Preferred in cases of moderate to severe neuroborreliosis
Syphilis	Aqueous crystalline penicillin G (IV)	3–4 million units every 4 h	200,000-300,000 units/kg/day in divided doses every 4–6 h	10–14 days	Hypersensitivity and anaphylactic reactions Diarrhea Anemia, leukopenia, thrombocytopenia Seizure	Further treatment with benzathine penicillin (2.4 million units IM once per week for 3 weeks) can be considered after initial neurosyphilis treatment to ensure eradication in adults
Intraocular *Mycobacterium tuberculosis*	Rifampin	10 mg/kg daily (typically 600 mg)	10–20 mg/kg daily	8 + 18 weeks (min)	Red/orange discoloration of body fluids Agranulocytosis DIC Hepatotoxicity Hypersensitivity reaction	Must be used with other agents or resistance likely to develop. Drug-drug interactions prevalent.
	Isoniazid	5 mg/kg daily (typically 300 mg)	5 mg/kg daily (estimated)	8 + 18 weeks (min)	Hepatotoxicity Peripheral neuropathy	Peripheral neuropathy from pyridoxine deficiency may be prevented with supplementation of 50 mg vitamin B6 daily
	Pyrazinamide	Weight based 40–55 kg = 1 g 56–75 kg = 1.5 g 76–90 kg = 2 g (daily)	35 mg/kg daily	8 weeks	Hepatotoxicity Gastrointestinal intolerance Gout exacerbation, arthralgia	May obtain serum uric acid in patients with history of gout.
	Ethambutol	Weight based (daily) 40–55 kg = 800 mg 56–75 kg = 1200 mg 76–90 kg = 1600 mg	20 mg/kg daily	8 weeks	Optic neuritis Optic atrophy Optic disc edema Central scotoma Red-green dyschromatopsia Gastrointestinal intolerance	Ocular adverse effects are less common in patients taking < 15 mg/kg and may be reversible after stopping the medication.

Adult doses are the maximum doses to be given and all doses assume normal renal function

CNS central nervous system, *DIC* disseminated intravascular coagulation, *HIV/AIDS* human immunodeficiency virus/acquired immunodeficiency syndrome, *IV* intravenous, *IM* intramuscular, *min* minimum

**Doxycycline is typically avoided in children less than 8 years old for concern of irreversible dental staining, although this may not occur with a short course of treatment

neuroretinitis. The strongest evidence for adjunctive use of corticosteroids comes from the multicenter retrospective cohort study of 86 patients with ocular manifestations due to CSD, which demonstrated an improvement in visual acuity of three lines or more in patients treated with the combination of antibiotic and corticosteroid (14/16 patients [88%]) compared to antibiotic alone (12/24 patients [50%]) [45•]. However, this was a retrospective study with a potential selection bias influencing the choice of treatment. In addition, the majority of the case reports in the literature, including the eight cases of intravenous and/or oral prednisone in the retrospective review by Chi et al. [60], showed no benefit in CSD optic neuropathy. Given the significant morbidity associated with systemic corticosteroids (including infection, hypertension, osteoporosis, diabetes mellitus, peptic ulcer disease, and avascular necrosis), and the lack of convincing benefit, routine use of systemic corticosteroids is not recommended in most cases of infectious neuroretinitis. However, the potent anti-inflammatory effects of systemic corticosteroids could theoretically offer some benefit in severe cases and therefore may be reserved for those patients with profound vision loss, fulminant optic disc edema, or significant intraocular inflammation. For example, a four to six-week corticosteroid taper is often used in addition to anti-mycobacterial therapy in patients with intraocular MTB and may improve outcomes [73, 77].

Recurrent idiopathic neuroretinitis

Similar to infectious neuroretinitis, few case series and retrospective reviews have been published examining the role of chronic immunosuppression for recurrent idiopathic neuroretinitis. In a case series of seven patients with recurrent neuroretinitis who received prompt treatment with oral or intravenous corticosteroids, there was no improvement in visual acuity or visual field [34]. Interestingly, one patient had no recurrence for three years while on azathioprine but then developed an acute attack upon discontinuation. In contrast, Purvin et al. performed a retrospective review of seven patients with recurrent idiopathic neuroretinitis treated with oral prednisone and/or azathioprine and found a 72% reduction in recurrent attacks per year after starting immunosuppressive therapy [33]. Several years later, the same group published a follow-up retrospective study that included four patients from the prior study and nine new patients and found that long-term immunosuppression with azathioprine (50 to 150 mg/day) and/or oral prednisone (10 mg every other day) resulted in the same 72% reduction in recurrent attacks per year [35]. Of note, the use of corticosteroids acutely following an attack did not appear to be of benefit in these patients. Therefore, based on the available published data, we recommend patients who have had at least two episodes of idiopathic neuroretinitis be initiated on immunosuppressive therapy in an attempt to reduce the number of attacks and preserve vision. Currently, azathioprine seems to be the first line medication, but newer and more potent agents may be more efficacious but have yet to be studied.

Emerging treatments

Although idiopathic neuroretinitis is typically a self-limited disease with most patients experiencing excellent visual recovery without treatment, there are

some patients that have recurrent disease resulting in irreversible visual loss [5, 27, 78]. It is this latter group that stands to gain the greatest amount in the quest for more effective treatment modalities.

Intravitreal approach

Angiogenesis is characteristic of *Bartonella* infection; therefore, anti-vascular endothelial growth factor (VEGF) therapy has the potential to be an effective treatment strategy [79]. A case report described the use of intravitreal triamcinolone plus anti-VEGF in a patient with idiopathic neuroretinitis with return of normal visual acuity and resolution of both the macular and optic disc edema [80].

Intraocular steroid injections and implants are another possible emerging treatment for neuroretinitis. A short acting dexamethasone (Ozurdex®, Allergan, Madison, NJ) implant or triamcinolone intravitreal injection could theoretically help reduce intraocular inflammation and macular edema. A longer acting agent like the recently US Food and Drug Administration (FDA)-approved three-year fluocinonide acetate implant (Yutiq®, EyePoint Pharmaceuticals, Watertown, MA) could help prevent recurrences. Dexamethasone implants have been used in cases of IRVAN and have showed some promise in treating the macular edema [81–83].

Immunosuppressive agents

There have been no studies which have evaluated the role of immunosuppressive medications such as rituximab, tumor necrosis factor (TNF) inhibitors, or other monoclonal antibodies in recurrent idiopathic neuroretinitis. A case report did demonstrate improvement in visual acuity and retinal exudation after administration of infliximab in two cases of IRVAN that were refractory to high-dose corticosteroids [84].

Chemotherapeutic agents

The immune check point inhibitor ipilimumab (an anti-cytotoxic T lymphocyte antigen-4 monoclonal antibody) has been linked to one case of bilateral neuroretinitis [31] and two cases of optic neuropathy [30•]. This class of medications disinhibits the immune system in order to help recognize self-antigens typically expressed in higher quantities on neoplastic cells, but with the collateral adverse activity of creating a state of autoimmunity. In the case of ipilimumab induced neuroretinitis, the medication was discontinued and a combination of topical and oral corticosteroid therapy was given with resolution of the ocular inflammation and improved vision over two months [31]. Accordingly, the mainstay of treatment for neuroretinitis secondary to the use of biologic agents, including checkpoint inhibitors and other chemotherapeutic regimens such as procarbazine and carmustine, involves discontinuation of the offending agent(s) and administration of topical and/or systemic corticosteroids over a period of weeks to months [85]. The duration and taper of the steroid therapy will depend on the clinical course of the patient and the expected elimination half-life of the causative medication, which for ipilimumab is 14.7 days [85].

Conclusion

Infectious neuroretinitis has many causes, and therefore, a targeted diagnostic evaluation must be undertaken to elucidate a specific cause in order to initiate a clearly defined treatment strategy. In cases of *Bartonella henselae*–associated neuroretinitis, immunocompetent patients with mild to moderate visual loss may be observed as the expected visual outcome is favorable. Empiric treatment may be considered in patients with a history suggestive of CSD while diagnostic tests are pending. Treatment is recommended for those with moderate to severe systemic symptoms, immunosuppressed patients, and those with severe vision loss. The preferred regimen is a four to six-week course of oral doxycycline and rifampin. Azithromycin may be used as an alternative to doxycycline, and in patients with documented allergy, ciprofloxacin or trimethoprim-sulfamethoxazole may be considered. There is no conclusive evidence that corticosteroid therapy is beneficial in infectious neuroretinitis, and because of the potential for significant adverse events, it should not be given routinely. However, corticosteroids can be used as an adjunct to antimicrobial therapy for cases with severe vision loss, significant optic disc edema, and a high degree of intraocular inflammation. Patients with an identified cause of infectious neuroretinitis (Lyme disease, syphilis, etc.) should receive the appropriate targeted therapy.

For patients with recurrent idiopathic neuroretinitis, high-dose intravenous and/or oral corticosteroid therapy with transition to an immunosuppressive agent are recommended to prevent recurrence and further loss of vision. To date, only azathioprine has been reported in the literature, but for patients with thiopurine methyltransferase (TMPT) deficiency, or for those with recurrences despite azathioprine use, newer immunosuppressive agents like rituximab and possibly other monoclonal antibodies may be beneficial.

Finally, intravitreal anti-VEGF therapy and implantable or injectable ocular corticosteroid therapies have theoretical, but not proven, efficacy and could result in severe complications, including endophthalmitis, and are therefore not currently recommended in the treatment of neuroretinitis. Further research involving the use of these agents may provide additional treatment options and greater insight into the pathophysiology of neuroretinitis.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
Dr. Bhatti participated in the following two studies that involved human subjects: Schmalfuss IM, Dean CW, Sistrom C, Bhatti MT. Optic neuropathy secondary to cat scratch disease: distinguishing MR imaging features from other types of optic neuropathies. AJNR Am J Neuroradiol. 2005;26 (6):1310–6; Chi SL, Stinnett S, Eggenberger E, Foroozan R, Golnik K, Lee MS, et al. Clinical characteristics in 53 patients with cat scratch optic neuropathy. Ophthalmology. 2012;119 (1):183–7.

Appendix

Note: Specific antibiotic dosing is provided in Table 2.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Abdelhakim A, Rasool N. Neuroretinitis: a review. Curr Opin Ophthalmol. 2018;29(6):514–9.

The most up-to-date review on all aspects of neuroretinitis including the different etiologies as well as treatment options. The authors discuss the pros and cons of antibiotics vs no antibiotics for the management of cat scratch neuroretinitis.

2. Pahor D. Leber's idiopathic stellate neuroretinitis. Can J Ophthalmol. 2001;36(6):347–9.
3. Gass JD. Diseases of the optic nerve that may simulate macular disease. Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol. 1977;83(5):763–70.
4. Kitamei H, Suzuki Y, Takahashi M, Katsuta S, Kato H, Yokoi M, et al. Retinal angiography and optical coherence tomography disclose focal optic disc vascular leakage and lipid-rich fluid accumulation within the retina in a patient with leber idiopathic stellate neuroretinitis. J Neuroophthalmol. 2009;29(3):203–7.
5. Maitland CG, Miller NR. Neuroretinitis. Arch Ophthalmol. 1984;102(8):1146–50.
6. Celiker H, Kazokoglu H, Eraslan M, Cerman E, Karabas L. Bartonella henselae neuroretinitis in patients without cat scratch. Jpn J Infect Dis. 2018;71(6):397–401.
7. Narayan SK, Kaliaperumal S, Srinivasan R. Neuroretinitis, a great mimicker. Ann Indian Acad Neurol. 2008;11(2):109–13.
8. Vaphiades MS. Rocky Mountain Spotted Fever as a cause of macular star figure. J Neuroophthalmol. 2003;23(4):276–8.
9. Reche-Sainz JA, Gracia Garcia-Miguel MT, Perez-Jacoiste MA. Papillitis and neuroretinitis of tuberculous etiology. Arch Soc Esp Oftalmol. 2019.
10. Fusco R, Magli A, Guacci P. Stellate maculopathy due to Salmonella typhi. A case report. Ophthalmologica. 1986;192(3):154–8.
11. Guliani BP, Kumar S, Chawla N, Mehta A. Neuroretinitis as presenting and the only presentation of Lyme disease: diagnosis and management. Indian J Ophthalmol. 2017;65(3):250–2.
12. Shoeibi N, Hosseini SM, Bayani R. Toxoplasmosis neuroretinitis: a case report. Iran Red Crescent Med J. 2016;18(4):e33115.
13. Basumatary LJ, Das S, Das M, Goswami M, Kayal AK. Leptospirosis presenting as neuroretinitis. J Neurosci Rural Pract. 2012;3(2):224–6.
14. Besirli CG, Elner SG. Retinal vasculitis in Toxocara canis neuroretinitis. J Ophthalmic Inflamm Infect. 2013;3(1):5.
15. Choi RY, Lauer A, Rosenbaum JT. Molecular diagnosis and ocular imaging of varicella zoster virus associated neuroretinitis. Am J Ophthalmol Case Rep. 2018;11:146–8.
16. Hsia YC, Chin-Hong PV, Levin MH. Epstein-Barr virus neuroretinitis in a lung transplant patient. J Neuroophthalmol. 2017;37(1):43–7.
17. Johnson BL, Wisotzkey HM. Neuroretinitis associated with herpes simplex encephalitis in an adult. Am J Ophthalmol. 1977;83(4):481–9.
18. Sivakumar RR, Prajna L, Arya LK, Muraly P, Shukla J, Saxena D, et al. Molecular diagnosis and ocular imaging of West Nile virus retinitis and neuroretinitis. Ophthalmology. 2013;120(9):1820–6.
19. Panday A, Sandy S, King D, Ramdeen S. A case of suspected symptomatic Zika Neuroretinitis. IDCases. 2017;9:104–5.
20. Davila PJ, Toledo A, Ulloa-Padilla JP, Izquierdo NJ, Emanuelli A. Unilateral neuroretinitis as a late-onset manifestation of the chikungunya fever: a case series. Retin Cases Brief Rep. 2017:1.
21. Ray S, Gragoudas E. Neuroretinitis. Int Ophthalmol Clin. 2001;41(1):83–102.
22. Fine M, Flocks M. Bilateral acute neuroretinitis with sarcoidosis treated with corticotropin and cortisone. AMA Arch Ophthalmol. 1953;50(3):358–62.
23. Matsuda A, Chin S, Ohashi T. A case of neuroretinitis associated with long-standing polyarteritis nodosa. Ophthalmologica. 1994;208(3):168–71.
24. Aigbe N, Bennouk Y, Madzou M, El Asri F, Chergui K, Brahime F, et al. Bilateral neuroretinitis secondary to

Takayasu's arteritis in a young girl. J Fr Ophtalmol. 2015;38(5):e89.
25. Santra G, Das I. Systemic lupus erythematosus presenting as neuroretinitis. J Assoc Physicians India. 2015;63(10):77–8.
26. Pellegrini F, Interlandi E, Prosdocimo G. Vogt-Koyanagi-Harada disease presenting as unilateral neuroretinits. Neuroophthalmology. 2018;42(1):11–6.
27. Purvin V, Sundaram S, Kawasaki A. Neuroretinitis: review of the literature and new observations. J Neuroophthalmol. 2011;31(1):58–68.
28. Saito M, Saito W, Kanda A, Ohguro H, Ishida S. A case of paraneoplastic optic neuropathy and outer retinitis positive for autoantibodies against collapsin response mediator protein-5, recoverin, and alpha-enolase. BMC Ophthalmol. 2014;14:5.
29.• Lee AR, El-Dairi MA. Anti-myelin oligodendrocyte glycoprotein optic neuritis or neuroretinitis? JAMA Ophthalmol. 2018;136(10):e182928.
This case report highlights a patient with neuroretinitis who was discovered to have anti-MOG antibodies, indicating that anti-MOG ought to be excluded before labeling patients with idiopathic disease.
30.• Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. CHECKPOINT INHIBITOR IMMUNE THERAPY: systemic indications and ophthalmic side effects. Retina. 2018;38(6):1063–7.
In this review, the authors highlight the ophthalmic complications of the newer chemotherapy agents, checkpoint inhibitors, including neuroretinitis.
31. Hahn L, Pepple KL. Bilateral neuroretinitis and anterior uveitis following ipilimumab treatment for metastatic melanoma. J Ophthalmic Inflamm Infect. 2016;6(1):14.
32. Bajgai P, Katoch D, Dogra MR, Singh R. Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome: clinical perspectives. Clin Ophthalmol. 2017;11:1805–17.
33. Purvin V, Ranson N, Kawasaki A. Idiopathic recurrent neuroretinitis: effects of long-term immunosuppression. Arch Ophthalmol. 2003;121(1):65–7.
34. Purvin VA, Chioran G. Recurrent neuroretinitis. Arch Ophthalmol. 1994;112(3):365–71.
35. Sundaram SV, Purvin VA, Kawasaki A. Recurrent idiopathic neuroretinitis: natural history and effect of treatment. Clin Exp Ophthalmol. 2010;38(6):591–6.
36. Habot-Wilner Z, Zur D, Goldstein M, Goldenberg D, Shulman S, Kesler A, et al. Macular findings on optical coherence tomography in cat-scratch disease neuroretinitis. Eye (Lond). 2011;25(8):1064–8.
37. Stewart MW, Brazis PW, Barrett KM, Eidelman BH, Mendez JC. Optical coherence tomography in a case of bilateral neuroretinitis. J Neuroophthalmol. 2005;25(2):131–3.
38. Zatreanu L, Sibony PA, Kupersmith MJ. Optical coherence tomography in neuroretinitis: epipapillary infiltrates and retinal folds. J Neuroophthalmol. 2017;37(2):176–8.
39. Yamanuha JJYMM. Bartonella neuroretinitis: a case report with new insights from fundus autofluorescence. J Clin Exp Ophthalmol. 2014:445.
40. Williams KE, Johnson LN. Neuroretinitis in patients with multiple sclerosis. Ophthalmology. 2004;111(2):335–40. discussion 40-1.
41. Parmley VC, Schiffman JS, Maitland CG, Miller NR, Dreyer RF, Hoyt WF. Does neuroretinitis rule out multiple sclerosis? Arch Neurol. 1987;44(10):1045–8.
42. Reddy AK, Morriss MC, Ostrow GI, Stass-Isern M, Olitsky SE, Lowe LH. Utility of MR imaging in cat-scratch neuroretinitis. Pediatr Radiol. 2007;37(8):840–3.
43. Schmalfuss IM, Dean CW, Sistrom C, Bhatti MT. Optic neuropathy secondary to cat scratch disease: distinguishing MR imaging features from other types of optic neuropathies. AJNR Am J Neuroradiol. 2005;26(6):1310–6.
44. Breitschwerdt EB. Bartonellosis: one health perspectives for an emerging infectious disease. ILAR J. 2014;55(1):46–58.
45.• Habot-Wilner Z, Trivizki O, Goldstein M, Kesler A, Shulman S, Horowitz J, et al. Cat-scratch disease: ocular manifestations and treatment outcome. Acta Ophthalmol. 2018;96(4):e524–e3.
Multicenter review of over 100 eyes that highlights the common ophthalmic manifestations of CSD. Additionally, the authors suggest antibiotics plus steriods improved acuity better than antibiotics alone.
46. Suhler EB, Lauer AK, Rosenbaum JT. Prevalence of serologic evidence of cat scratch disease in patients with neuroretinitis. Ophthalmology. 2000;107(5):871–6.
47. Reed JB, Scales DK, Wong MT, Lattuada CP Jr, Dolan MJ, Schwab IR. Bartonella henselae neuroretinitis in cat scratch disease. Diagnosis, management, and sequelae. Ophthalmology. 1998;105(3):459–66.
48. Gulati A, Yalamanchili S, Golnik KC, Lee AG. Cat scratch neuroretinitis: the role of acute and convalescent titers for diagnosis. J Neuroophthalmol. 2012;32(3):243–5.
49. Hage CA, Azar MM, Bahr N, Loyd J, Wheat LJ. Histoplasmosis: up-to-date evidence-based approach to diagnosis and management. Semin Respir Crit Care Med. 2015;36(5):729–45.
50. Bass JW, Freitas BC, Freitas AD, Sisler CL, Chan DS, Vincent JM, et al. Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch disease. Pediatr Infect Dis J. 1998;17(6):447–52.
51. Margileth AM. Antibiotic therapy for cat-scratch disease: clinical study of therapeutic outcome in 268 patients and a review of the literature. Pediatr Infect Dis J. 1992;11(6):474–8.

52. Pitassi LH, Magalhaes RF, Barjas-Castro ML, de Paula EV, Ferreira MR, Velho PE. Bartonella henselae infects human erythrocytes. Ultrastruct Pathol. 2007;31(6):369–72.
53. Golnik KC, Marotto ME, Fanous MM, Heitter D, King LP, Halpern JI, et al. Ophthalmic manifestations of Rochalimaea species. Am J Ophthalmol. 1994;118(2):145–51.
54. Curi AL, Machado D, Heringer G, Campos WR, Lamas C, Rozental T, et al. Cat-scratch disease: ocular manifestations and visual outcome. Int Ophthalmol. 2010;30(5):553–8.
55. Bhatti MT, Lee MS. Should patients with bartonella neuroretinitis receive treatment? J Neuroophthalmol. 2014;34(4):412–6.
56. Conrad DA. Treatment of cat-scratch disease. Curr Opin Pediatr. 2001;13(1):56–9.
57. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of Bartonellosis. Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2017 [updated 05/07/2017. 1-5]. Available from: https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/329/bartonellosis. Accessed 1 May 2019.
58. Rosen BS, Barry CJ, Nicoll AM, Constable IJ. Conservative management of documented neuroretinitis in cat scratch disease associated with Bartonella henselae infection. Aust N Z J Ophthalmol. 1999;27(2):153–6.
59. Solley WA, Martin DF, Newman NJ, King R, Callanan DG, Zacchei T, et al. Cat scratch disease: posterior segment manifestations. Ophthalmology. 1999;106(8):1546–53.
60. Chi SL, Stinnett S, Eggenberger E, Foroozan R, Golnik K, Lee MS, et al. Clinical characteristics in 53 patients with cat scratch optic neuropathy. Ophthalmology. 2012;119(1):183–7.
61. Centers for Disease Control and Prevention - Bartonella infection (cat scratch disease, trench fever, and Carrión's disease) 2014 [updated 12/14/2015]. Available from: https://www.cdc.gov/bartonella/clinicians/index.html. Accessed 1 May 2019.
62. Attawan A, Pepper IM, Hickman SJ. The natural history of idiopathic neuroretinitis. Pract Neurol. 2015;15(5):387–8.
63. Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review. JAMA. 2016;315(16):1767–77.
64. Centers for Disease Control and Prevention - Lyme disease 2018 [updated 12/21/2018. Available from: https://www.cdc.gov/lyme/treatment/index.html. Accessed 1 May 2019.
65. Hu LT. Lyme disease. Ann Intern Med. 2016;164(9):ITC65–80.
66. Ljostad U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. Lancet Neurol. 2008;7(8):690–5.
67. The diagnosis, management and prevention of syphilis: an update and review – a clinical guidance document for use in the diagnosis and management of syphilis. Based on content from the 2015 CDC STD treatment guidelines, and developed by the NYC Department of Health and Mental Hygiene Bureau of Sexually Transmitted Infections and the NYC STD Prevention Training Center. March 2019.
68. Centers for Disease Control and Prevention - 2015 Sexually transmitted diseases treatment guidelines: Syphilis.2015.
69. Arruga J, Valentines J, Mauri F, Roca G, Salom R, Rufi G. Neuroretinitis in acquired syphilis. Ophthalmology. 1985;92(2):262–70.
70. Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. JAMA. 2014;312(18):1905–17.
71. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147–e95.
72. American Thoracic S, Cdc, Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep. 2003;52(RR-11):1–77.
73. Cutrufello NJ, Karakousis PC, Fishler J, Albini TA. Intraocular tuberculosis. Ocul Immunol Inflamm. 2010;18(4):281–91.
74. Biggs HM, Behravesh CB, Bradley KK, Dahlgren FS, Drexler NA, Dumler JS, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain Spotted Fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis - United States. MMWR Recomm Rep. 2016;65(2):1–44.
75. Brett-Major DM, Coldren R. Antibiotics for leptospirosis. Cochrane Database Syst Rev. 2012;(2):CD008264.
76. Todd SR, Dahlgren FS, Traeger MS, Beltran-Aguilar ED, Marianos DW, Hamilton C, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain Spotted Fever. J Pediatr. 2015;166(5):1246–51.
77. Gupta V, Gupta A, Rao NA. Intraocular tuberculosis–an update. Surv Ophthalmol. 2007;52(6):561–87.
78. Dreyer RF, Hopen G, Gass JD, Smith JL. Leber's idiopathic stellate neuroretinitis. Arch Ophthalmol. 1984;102(8):1140–5.
79. Kirby JE. In vitro model of Bartonella henselae-induced angiogenesis. Infect Immun. 2004;72(12):7315–7.
80. Cakir M, Cekic O, Bozkurt E, Pekel G, Yazici AT, Yilmaz OF. Combined intravitreal bevacizumab and triamcinolone acetonide injection for idiopathic

neuroretinitis. Ocul Immunol Inflamm. 2009;17(3):221–3.
81. Empeslidis T, Banerjee S, Vardarinos A, Konstas AG. Dexamethasone intravitreal implant for idiopathic retinal vasculitis, aneurysms, and neuroretinitis. Eur J Ophthalmol. 2013;23(5):757–60.
82. Saatci AO, Ayhan Z, Takes O, Yaman A, Bajin FM. Single bilateral dexamethasone implant in addition to panretinal photocoagulation and oral azathioprine treatment in IRVAN syndrome. Case Rep Ophthalmol. 2015;6(1):56–62.
83. Chong YJ, Logeswaran A, Sarmad A, Damato EM. Idiopathic retinal vasculitis, aneurysms and neuroretinitis (IRVAN): case series of three patients with multimodal imaging. Graefes Arch Clin Exp Ophthalmol. 2019;257(5):1013–8.
84. Cheema RA, Al-Askar E, Cheema HR. Infliximab therapy for idiopathic retinal vasculitis, aneurysm, and neuroretinitis syndrome. J Ocul Pharmacol Ther. 2011;27(4):407–10.
85. Fellner C. Ipilimumab (yervoy) prolongs survival in advanced melanoma: serious side effects and a hefty price tag may limit its use. P T. 2012;37(9):503–30.

Publisher's Note