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Chapter

Retinitis Due to Infections

Ruben Rose, Alexey Gorin, Mathias Voß and Helmut Fickenscher

Abstract

Infections are a major cause for retinitis. Whereas Varicella-Zoster and Herpes Simplex viruses are the major reason for acute retinal necrosis, cytomegalovirus retinitis typically occurs in immunocompromised patients. Toxoplasmosis and toxocariasis are the major parasitic pathogens affecting the retina and adjacent tissues. Among the bacterial causes, tuberculosis, syphilis, and bartonellosis are discussed as retinal diseases. The emphasis is laid on the epidemiological and clinical peculiarities, the respective diagnostic procedures, and the therapeutic approaches. Moreover, global disease aspects of infectious retinitis are included.

Keywords: acute retinal necrosis, bartonellosis, chorioretinitis, cytomegalovirus, toxocariasis, toxoplasmosis, tuberculosis, retinitis, syphilis, varicella zoster virus

1. Introduction

Retinitis can present in various different forms. Some of them are rather specific for individual pathogens, whereas other phenotypes are rather overlapping (**Table 1**). In this manuscript, the major viral, parasitic, and bacterial pathogens are presented and discussed together with the different clinical manifestations.

Disease form	Main pathogens
Acute retinal necrosis	VZV, HSV
Cytomegalovirus retinitis	CMV
Chorioretinitis	<i>Toxoplasma gondii</i> , <i>Treponema pallidum</i>
Chorioiditis with retinitis	Mycobacteria, Toxocara, <i>T. pallidum</i>

Table 1.
Classification of retinitis and related disease forms.

2. Virus-induced retinitis

2.1 Acute retinal necrosis

Acute retinal necrosis (ARN) is an infectious inflammation of the retina, the vitreous and the anterior chamber of the eye that can lead to blindness by destruction of the optic nerve and retina in immune competent individuals. The first clinical

reports were published by Urayama in 1971 under the designation Kirisawa uveitis. In 1978, the term acute retinal necrosis was introduced by Young and Bird [1, 2].

2.1.1 Pathogen

ARN is primarily caused by the α -herpesviruses Varicella-Zoster virus (VZV) or Herpes-Simplex virus (HSV) 1 and 2, which together account for 97% of cases (95%-confidence interval (CI) 96–99%). Among ARNs caused by α -herpesviruses, VZV is the leading cause at 69% (95%-CI 60–76%), followed by HSV-2 and HSV-1. α -herpesviruses carry a large double-stranded DNA genome and establish latency in the nuclei of the sensory and autonomic spinal ganglia of the central nervous system after primary infection. Normally, the virus genome is latently maintained in the sensory ganglia since lytically infected cells are rapidly eliminated by the CD8-positive cytotoxic killer cells of the immune system. The virus genomes persist latently in the nuclei of the sensory neurons in circular extrachromosomal form as episomes. Viral reactivation occurs due to poorly defined stressors such as ultraviolet light, neurosurgical procedures, or steroid or immunosuppressive therapy. Virus reactivation is followed by peripheral viral replication and usually results in herpes zoster, herpes orofacialis, herpes genitalis, or in rare cases also in zoster ophthalmicus or herpes oculi [2, 3].

The roles in ARN development of the β -herpesvirus cytomegalovirus (CMV) and the γ -herpesvirus Epstein–Barr virus (EBV), which establish their latency within myeloid stem cells and quiescent B lymphocytes, respectively, are still controversial. While at least some cases have been reported in which CMV appears to be causal for ARN, EBV has only been detected in some cases in addition to VZV and does not appear to play a causative role in immunocompetent individuals [3, 4].

2.1.2 Epidemiology

ARN is a very rare disease, which affects one individual per 1.5–2.0 million persons per year. In a meta-analysis, men were shown to have a slightly higher risk to be affected by ARN than women [3]. Interestingly, the age of manifestation of ARN depends on the responsible virus species. Patients with ARN due to VZV or HSV-2 have a median age of 48.8 and 47.8 years, respectively, whereas patients with ARN due to HSV-1 have a median age of only 31.1 years [3]. In addition, ARN shows two peaks of manifestation age, the first at age of approximately 20 years and the second at age 50 [4]. In addition, some studies have shown that certain human leukocyte antigen (HLA) types such as HLA-DQw7 as well as HLA phenotype Bw62, DR4, and HLA-DR9 are associated with the occurrence of ARN or its severity, respectively [5, 6].

2.1.3 Clinical peculiarities

Characteristic of ARN is an inflammation of the anterior chamber and vitreous associated with peripheral necrotizing retinitis with focal necrotic lesions that become circular as the disease progresses to the posterior pole. This process is additionally associated with an occlusive vasculitis that leads to arteriolar narrowing. This first phase is followed by a second phase in which retinal atrophy, proliferative vitreoretinopathy, and retinal detachment occur [4]. While some studies have found ARN to be unilateral in nearly 90% of cases, other studies report bilateral involvement in up to one-third of cases [2–4]. In any case, ARN that initially occurs unilaterally may spread to the contralateral eye.

In contrast to ARN, progressive outer retinal necrosis (PORN), now considered a variant of ARN, affects almost exclusively immunocompromised individuals, *e.g.*, human immunodeficiency virus (HIV)-infected individuals in the AIDS stage or organ transplant recipients. It results from reactivation of VZV and spreads extremely rapidly to the deep retinal layers, leading to retinal detachment. However, PORN lacks the vasculitis aspect of classic ARN [2, 4].

2.1.4 Diagnosis

According to the American Uveitis Society, ARN is defined by the following criteria: (1) “focal, well-demarcated areas of retinal necrosis in the peripheral retina (outside the major temporal vascular arcs)”; (2) “rapid, circumferential progression of necrosis (if antiviral therapy has not been administered)”; (3) “evidence of occlusive vasculopathy”; (4) “a marked inflammatory reaction in the vitreous”; and (5) in the “anterior chamber.” In addition, symptoms such as optic atrophy, scleritis, and pain are common but not essential [7]. These criteria were established before molecular biological detection methods such as polymerase chain reaction (PCR) were widely available. Therefore, a recent publication proposed a modification of the diagnostic criteria to include serological and PCR-based methods with respect to the responsible viruses. By comparing the antibody concentration against the different herpesviruses in serum with the antibody concentration in vitreous fluid, the Goldmann-Witmer coefficient (GWC) can be determined. A positive GWC is highly specific (100%) at a moderate sensitivity of only 33%. Detection by PCR is both highly sensitive (95%) and only slightly less specific (92%) [8]. Identification of the specific virus is important, as it has therapeutic consequences. The use of PCR-based detection methods has the additional advantage of enabling the identification of viral resistance to the antiviral drugs used by genotyping [9, 10]. Imaging of the eye such as fundus fluorescein angiography or optical coherence tomography is useful to determine the extent and progression of the disease [4].

2.1.5 Therapy

Since the goal of therapy is to inhibit further disease progression driven by viral replication, antiviral therapy should be initiated immediately after clinical diagnosis and not delayed by waiting for laboratory results. However, viral diagnostics are useful because therapy for CMV relies on different antiviral drugs than therapy for VZV, HSV-1, and HSV-2. In addition, as mentioned above, PCR diagnostics allow detection of resistance by genotyping and thus adjustment of therapy. This is particularly important for immunocompromised patients, who are affected, for example, by drug-resistant HSV-1 strains in up to 14% of cases, whereas this is only the case in less than 1% of immunocompetent individuals [11, 12].

The three α -herpesviruses VZV, HSV-1, HSV-2 are treatable with the antiviral drugs aciclovir and its prodrug valaciclovir, penciclovir, and its prodrug famciclovir, as well as by cidofovir and foscarnet. The prodrugs valaciclovir and famciclovir, which must be activated in enterocytes by the first-pass effect, have a good oral bioavailability of 54–60% and 77%, respectively, unlike aciclovir and penciclovir and, thus, can be efficiently administered orally. Aciclovir and penciclovir, as well as their prodrugs, are nucleoside analogs that must be activated by a viral enzyme called thymidine kinase (TK). After activation by viral TK, this group of antiviral drugs causes chain termination during viral replication. Because they act only in virus-infected

cells, they are well tolerated, especially in their oral formulation. Nevertheless, there are side effects, which often include headache, rash, and gastrointestinal symptoms in the oral formulations. However, intravenous use of aciclovir may result in neurotoxicity and renal toxicity due to crystalline nephropathy. Therefore, patients with impaired renal function must be treated with lower doses. Because the main cause of viral resistance are mutations within the viral TK, the rate of cross-resistance within this antiviral drug group is high. In case of resistance, cidofovir and foscarnet are alternatives that do not require viral TK activation. The nucleoside analog cidofovir is activated only by cellular kinases and, once activated, acts similarly to the other nucleoside analogs. The drug is excreted exclusively by the kidneys and is nephrotoxic and, therefore, requires renal protection by probenecid administration. Foscarnet, a pyrophosphate analog, directly inhibits the viral polymerase by blocking its pyrophosphate-binding site. The most important side effect of foscarnet is nephrotoxicity. Therefore, the dose must be adjusted in patients with impaired renal function. Both foscarnet and cidofovir must be administered intravenously due to their low oral bioavailability of 20% and 5%, respectively; recommended dosing is 60 mg/kg three times daily and 5 mg/kg over 1 h once weekly for 2 weeks [2, 12].

Traditionally, therapy for ARN consisted of administration of 10 mg/kg aciclovir three times daily or 1500 mg/m² per day intravenously for 5–14 days. This should be followed by oral treatment with 800 mg of aciclovir five times daily for 6 weeks, as such treatment has been shown to prevent 90% of contralateral eye infections [2, 4]. However, it has been shown that similar plasma concentrations can be achieved by oral administration of valaciclovir as by intravenous administration of aciclovir, and the visual outcome does not appear to be worse. Therefore, efforts are being made to avoid intravenous therapy completely. Currently, oral therapy regimens with 2000 mg valaciclovir or 500 mg famciclovir three times daily are being used [4, 12]. Regarding the duration of follow-up, some authors recommend extending therapy with 800 mg of aciclovir or 1000 mg of valaciclovir three times daily for 6–12 months, followed by lifelong use of 1000 mg of valaciclovir daily to prevent infestation of the contralateral eye or relapse [12]. During the initial therapy phase, intravitreal use of 2.4 mg/0.1 ml foscarnet or 2.0/0.1 ml ganciclovir two times per week in combination with systemic antiviral therapy appears to have therapeutic benefit [4, 12]. With respect to foscarnet, a recent systematic review based on case-control and cohort studies, as well as case series and case reports, also supports this therapeutic approach [13]. Because vasculitis and inflammation contribute to the progression of ARN, the use of systemic or topical steroids and anticoagulation drugs is under discussion. However, the evidence base for such treatments is low and must be used with caution [12]. In the case of a successful antiviral therapy, no further lesions should be observed from day 2 of therapy, from 4 to 5 days of therapy, the retinal infiltrate should tend to regress, and after 1 month, a complete remission should be observable [2].

Another highly controversial issue is the use of prophylactic procedures such as prophylactic vitrectomy or prophylactic laser retinopexy. It has been shown that the risk of rhegmatogenous retinal detachment after ARN can be significantly reduced by prophylactic vitrectomy [5]. This finding was confirmed by a recent meta-analysis of seven retrospective cohort studies, which included the study by Hillenkamp and colleagues [5, 14]. However, this meta-analysis found that visual outcome was significantly worse in the prophylactic vitrectomy group than in the control group treated with antiviral drugs only. The authors attributed this result to silicone oil tamponade and long-term complications in the vitrectomy group. Although there are also some small studies that see a benefit in terms of visual outcome, there is ultimately no

conclusive evidence to support such treatment [12]. Another much debated topic is whether prophylactic laser therapy can reduce the incidence of retinal detachment. Although a meta-analysis of 14 studies found that prophylactic laser retinopathy can significantly prevent retinal detachments after ARN [15], Powell et al. pointed out that prophylactic laser retinopathy is only possible if the vitreous media is clear enough, which means that often only the less severely affected eyes are treated with laser [12]. In addition, the cited meta-analysis by [15] did not examine the question of how the therapy affects visual outcome. Thus, the benefit of prophylactic laser retinopathy remains questionable.

For ARN caused by CMV that lacks TK and instead expresses the kinase UL97, ganciclovir and its orally better bioavailable prodrug valganciclovir, as well as cidofovir and foscarnet, are therapeutic options. Because of its low bioavailability of 5%, ganciclovir must be administered intravenously at a dose of 5 mg/kg. Alternatively, 900 mg of valganciclovir can be administered orally, which has an oral bioavailability of 60%. Because ganciclovir and its prodrug cause neutropenia in approximately 8% of patients, the blood values of patients treated with either of these drugs should be monitored regularly. Cidofovir and foscarnet are alternatives in case of viral resistance to ganciclovir or its prodrug, which is mostly caused by mutations within the UL97 [2].

2.1.6 Prognosis

ARN has often a poor outcome, i.e., two-thirds of affected eyes achieve only a final best-corrected visual acuity of 6/60 or worse. Therefore, early diagnosis and urgent therapy are critical. In PORN, the outcome is even worse. Two-thirds of affected eyes are not even able to perceive light because they often do not respond well to antiviral therapy [4].

2.2 Cytomegalovirus retinitis

In immunocompetent persons, cytomegalovirus (CMV) normally leads only to a rather harmless anterior uveitis. However, in immunocompromised individuals, such as AIDS patients or those who have undergone organ transplantation, CMV can also lead to CMV retinitis, which is distinguishable from ARN but can also cause retinal detachment and blindness [16, 17].

2.2.1 Pathogen

CMV belongs to the beta-herpesviruses and has a large double-stranded DNA genome. It is transmitted perinatally or through any type of close contact via body fluids. The primary infection, which happens usually in young and healthy individuals, is typically mild or asymptomatic. However, primary infection of the pregnant woman may result in severe embryopathy or fetal death. After primary infection, the virus establishes latency within myeloid stem cells. In immunocompetent individuals, reaction is usually asymptomatic. A special but feared transmission of CMV can occur through organ transplantation [3, 4, 17, 18].

2.2.2 Epidemiology

Worldwide, CMV seroprevalence ranges from 60% to 100% and increases with age. In the United States, for example, 36.3% of children aged 6–11 years but 90.8% of

adults aged 80 years or older are infected. CMV retinitis affects males more often than females and can occur at any age. However, most cases occur between the ages of 30 and 60. Initially, CMV retinitis was particularly common in AIDS-stage HIV patients, but with the development and widespread use of antiretroviral therapy (ART), its incidence in the AIDS patient group decreased by over 90%, and clinical outcomes in affected individuals improved significantly [4, 17].

2.2.3 Clinical peculiarities

In immunocompetent individuals, CMV reactivation usually results in unilateral, relatively mild, recurrent anterior uveitis with anterior chamber inflammation, elevated intraocular pressure, stromal iris atrophy, and few granulomatous keratic precipitates [16]. However, especially in immunocompromised individuals, CMV can affect the retina and cause unilateral CMV retinitis. In 20% of cases, infection of the contralateral eye occurs over the next 6 months [17]. Retinitis usually consists of two stages. In the first stage, the active retinitis usually shows three types of retinal lesions: First, fulminant and edematous lesions consisting of extensive retinal hemorrhages preceding confluent retinal necrosis; second, indolent and granular lesions consisting of granular satellites with little or no hemorrhage; and third, exudative lesions based on angiitis with extensive vascular sheathing. The second stage is characterized by large necroses and retinal tears. Finally, there is retinal atrophy with fibrosis, calcification, and sclerotic vessels [4].

2.2.4 Diagnosis

The diagnosis of CMV retinitis is made by ophthalmoscopy and should be documented by digital fundus photography. PCR diagnostics can confirm CMV retinitis, which is important with regard to the chosen therapy, and allows monitoring of therapy response and detection of resistant CMV strains by genotyping [4, 12].

2.2.5 Therapy

For retinitis caused by CMV that lacks TK and instead expresses the kinase UL97, ganciclovir and its more orally bioavailable prodrug valganciclovir, as well as cidofovir and foscarnet, are therapeutic options. As mentioned above, ganciclovir and its prodrug cause neutropenia in approximately 8% of patients. Therefore, the blood of patients treated with either of these drugs should be monitored regularly. Cidofovir and foscarnet are alternatives in the event of viral resistance to ganciclovir or its prodrug, which in most cases is caused by mutations within the UL97 [12]. For the therapy of the CMV retinitis, the combination of intravitreal and systemic therapy is recommended [17].

Typical dosage for CMV retinitis therapy: intravenous ganciclovir, induction by 5 mg/kg 2× daily for 14–21 days, maintenance with 5 mg/kg/day; oral valganciclovir, induction by 900 mg 2× daily, maintenance 900 mg daily; intravenous foscarnet, 90 mg/kg 2× daily for 14 d, maintenance 120 mg/kg/day; intravenous cidofovir, 5 mg/kg weekly for 3 weeks, maintenance 5 mg/kg every 2 weeks.

Typical dosage for intravitreal CMV retinitis therapy: ganciclovir, induction by 2 mg 1–4× to stop retinitis, maintenance with 2 mg weekly; foscarnet, induction by 1.2–2.4 mg 1–2× weekly, maintenance with 1.2 mg weekly; cidofovir, induction by 20 µg 1–8×, maintenance with 20 µg every 5–6 weeks.

2.2.6 Prognosis

The consequences of CMV retinitis vary widely and include regression of retinal damage and complications such as retinal detachment or recurrence. In most cases, visual acuity stabilizes or improves, in many cases to complete remission [4].

3. Retinitis forms due to parasites

3.1 Ocular toxoplasmosis

Ocular toxoplasmosis is one of the most frequent causes for infectious uveitis globally, typically presenting as rather unilateral posterior uveitis with chorioretinal lesions and vitritis [19].

3.1.1 Pathogen

The ubiquitously distributed protozoon of the phylum Apicomplexa, *Toxoplasma (T.) gondii* is an obligate intracellular parasite, which invades host cells of a wide range of vertebral species including humans via an apical complex. Specific *T. gondii* genotypes are likely associated with higher prevalence and development of ocular toxoplasmosis [20]. Infection and transmission by *T. gondii* are possible in various stages of the parasitic life cycle. Soil-borne, water-borne, or food-borne uptake of oocysts containing infectious sporozoites and inoculation by tissue cysts containing tachyzoites with undercooked or raw meat, free tachyzoites in milk and eggs are the most common infectious routes besides vertical transmission, organ transplantation, and blood transfusion. *T. gondii* primary infects intestinal epithelial cells, circulates via the blood stream, performs extravasation by forming cysts [21, 22], and develops into different parasitic stages such as free infectious tachyzoites after intracellular replication and cell lysis or rather dormant and inactive encysted bradyzoites. The cell-invading and immune-escaping capacity of *T. gondii* is actively mediated by complex host-parasite interactions via surface ligands. Altered cytokine profiles of targeted macrophages, dendritic, and tissue cells, by intracellular *T. gondii* are the key to immune evasion, organ tropism, and the well balanced pro- and anti-inflammatory signaling of the targeted cells. These mechanisms consequently lead to a constant destructive and protective host tissue and parasite interaction in immunocompetent persons [23].

3.1.2 Epidemiology

Toxoplasmosis is widely spread with an approximately 30% human infection rate and wide geographical variation of seropositive rates up to 80% within certain populations [20, 24, 25]. Recent studies elucidated that endemic *T. gondii* strains play a major role in ocular toxoplasmosis prevalence. Archetypal strains I, II, III are dominant in Europe and North America, and non-archetypal strains are a minority but nevertheless cause the majority of ocular toxoplasmosis cases, approximately 1–2%, in immunocompetent seropositive individuals. In South America and Brazil, non-archetypal strains are dominant, and the ocular toxoplasmosis prevalence is up to 10–20% in the seropositive population [26, 27]. Other important factors related to the endemic seroprevalence of *T. gondii* are climate and socioeconomic factors such as access to clean and not contaminated water, public and institutional surveillance,

hygiene and control of parasitic prevalence in life stock and related food products, blood products, and individual host-dependent factors such as food consumption habits, age, and the host's immunocompetence.

Although seroprevalence in populations is rather high, the majority of infected people do not develop symptoms due to immunological parasite-host interactions. Ocular toxoplasmosis can occur month or years after postnatal or congenital infection and might be the first sign of a systemic toxoplasmosis. Therefore, all seropositive individuals are at risk to develop an ocular toxoplasmosis in their lifetime. Age over 40, time of infection, and immunosuppression are risk factors for onset, recurrence, and severity of ophthalmic toxoplasmosis [23].

3.1.3 Clinical peculiarities

In patients with ocular toxoplasmosis, retinochoroiditis is the most typical finding. Active intraocular inflammation often presents as focal necrotizing granulomatous retinitis with reactive granulomatous choroiditis and vitritis. The clinical image contains active lesions, often close to a pigmented or atrophic scar, described as whitish foci with obscure borders. Vasculitis can appear close or distant to the lesions and presents mainly as phlebitis and less frequent as arteritis eventually with hemorrhages [28]. In rare cases, Kyrieleis arteritis, a type of arteriolitis with intravascular nodular-like white plaques, can be found [29, 30]. Usually, the active lesions tend to heal within 2–4 month in immunocompetent patients by leaving an atrophic area gradually turning into a hyperpigmented scar due to disruption of retinal pigment epithelium. New active lesions are frequently close to old scars as a sign of recurrence [31]. Especially in immunocompromised patients, the differential diagnosis to other pathogens may be difficult [32].

Nonetheless, there are many atypical and unusual presentations related to the anatomical region of inflammation including anterior uveitis [28] with complication of rise in intraocular pressure, punctate outer retinal toxoplasmosis (PORT) with risk for secondary optic neuropathy and significant visual loss [23], neuroretinitis, and other unspecific features such as scleritis [33], which may delay a timely diagnosis [34] with risk of permanent vitreous opacities, deterioration in visual acuity or even vision loss in case of macular or optic nerve involvement. Recurrences with inflammatory reaction may occur at any time post primary infection resulting from ruptured intraretinal cysts.

Complications are associated with intraocular inflammation and are correlated with older age, retinal lesions larger than one disc size, and extra-macular lesions. Vasculitis-associated complications are proliferative tractional bands, vitreoretinopathy, and retinal vasculitis, which can contribute to tractional retinal detachment and hemorrhages and vascular occlusions. Especially immunocompromised patients with large necrotic areas are at higher risk for retinal cracks and retinal detachment [23].

3.1.4 Diagnostics

Typical ocular toxoplasmosis usually is diagnosed by characteristic clinical findings and serological detection methods. However, imaging technics help to estimate severity of clinical signs, diagnosing atypical ocular toxoplasmosis patterns and surveil the clinical course and treatment efficacy. The diagnostic work-up usually is composed of basic ophthalmological assessments, imaging techniques such as ultrasound, fundus color photography, optical coherence tomography, optical coherence tomography angiography, confocal scanning laser ophthalmoscopy, fundus autofluorescence,

fluorescent angiography, indocyanine green angiography, and direct and indirect *T. gondii* detection tests in case of uncertainty after fundus imaging. Therefore, serological methods, immunohistochemical methods, specific PCR methods are commonly used. High sensitivity and specificity of PCR-based assays and detection of specific antibodies from vitreous and aqueous fluid have gained remarkable diagnostic value in diagnosing ocular toxoplasmosis [23]. PCR is the main detection method for determining *T. gondii* infection in ocular inflammation, congenital infections, and immunocompromised patients including HIV-infected patients. Real-time PCR and nested-PCR show consistently good results in detecting parasite DNA in ocular fluids of patients with toxoplasmosis including immunocompromised with high sensitivity and specificity. Detection works best during the first weeks of onset of symptoms.

Serological laboratory tests routinely help to determine whether an infection is recently acquired or chronic according to individual course of IgM, IgG, and IgA titers and IgG avidity patterns. Additionally, serology helps to rule out toxoplasmosis if suspected. Low IgG and absence of IgM antibodies are the regular finding in immunocompetent individuals with typical ocular toxoplasmosis. This highlights that only positive IgG titers are not suitable to confirm the diagnosis. However, solely immune enzyme assays are useful in diagnosing active ocular toxoplasmosis by supporting clinical findings in up to 96% of typical and atypical ocular toxoplasmosis by indicating positivity and significant increase of specific antibodies titers [35]. The approach of combined PCR and antibody detection from aqueous humor has strong predictive power in confirming the clinical diagnosis of ocular toxoplasmosis especially in immunocompromised individuals and atypical cases [36]. Interferon- γ release assays from whole blood for specific *T. gondii* T-cells show reliable results in detecting toxoplasmosis with 96% sensitivity and 91% specificity in seropositive adults with acute or chronic infection and in 94% and 98% for infants with congenital infection by mothers who acquired infection during pregnancy [37, 38].

3.1.5 Therapy

When deciding whether to treat active retinochorioiditis, considerations should include the mostly benign natural course, patients' characteristics (pregnancy, newborns, allergies, etc.) toxicity of potential drugs, the individual clinical course and immune status, presentation of active lesions, visual acuity and vitreous opacity, complications such as vascular occlusion and edema of macular or optic disc. Treatment regimens are combinations of antimicrobial drugs (control of parasite replication) and topical and systemic corticosteroids for 4–6 weeks. The role of treatment in chronic toxoplasmosis remains unclear due to lack of evidence in efficacy against tissue cysts [39]. The main goals of treatment are size reduction of lesions and prevention of adverse complications of active ocular toxoplasmosis. All first-line regimens have no significant effect on recurrences although trimethoprim-sulfamethoxazole might have [40] if substituted for sulfadiazine. Close monitoring of drug-related gastrointestinal, dermatological, and hematological (leukocytopenia, thrombocytopenia) adverse events and allergic side effects is recommended. Weekly blood tests should be performed and depending on the chosen treatment regimen substitution of folic acid is required.

First-line regimens are: (I) pyrimethamine, sulfadiazine, folic acid, and prednisone; (II) pyrimethamine, clindamycin, folic acid, and prednisone; (III) pyrimethamine, sulfadiazine, clindamycin, folic acid, and prednisone “quadruple therapy.” Selected alternative regimens are: (IV) trimethoprim-sulfamethoxazole and

prednisone; (V) clindamycin, spiramycin, prednisone; (VI) clindamycin, sulfadiazine, prednisone; (VII) pyrimethamine, azithromycin, folic acid, prednisone. Other alternative combinations include atovaquone or tetracycline derivatives [41, 42].

The first-line treatments or called classical treatments show better reduction of duration of posterior pole retinitis in comparison to alternative regimens and are more fitting for foveal adjacent and fovea lesions [43]. Systemic corticosteroid therapy usually starts 3 days after and stops 10 days before antimicrobial therapy and is only recommended in immunocompetent individuals [23].

Another therapeutic approach is the intravitreal application of clindamycin and dexamethasone, which show larger lesion size reductions in IgM-positive patients compared with the classic treatment or no treatment. Additional advantages of intravitreal drug application are less systemic side effects what might be beneficial in pregnancy. One of the disadvantages is the risk of fulminant systemic disease in immunocompromised patients. Other supportive measurements include steroid eye drops, mydriatics, and local hypotensive agents to prevent and manage complications of active ocular toxoplasmosis [44]. For immunocompromised or pregnant patients, modified treatment strategies are available, which mostly aim at prevention of severe complications of active ocular toxoplasmosis and toxoplasmosis in general with indications to treat at low thresholds and close treatment supervision by a multidisciplinary team [23].

3.1.6 Prognosis

The prognosis and course are mainly dependent on the timely and appropriate diagnosis and management of active ocular toxoplasmosis, complications, and the frequency of individual recurrences associated with personal and environmental risk factors over time.

3.2 Ocular toxocariasis

Ocular toxocariasis or ocular larva migrans is a worldwide prevalent common zoonotic helminthic infection caused by roundworms, which might cause severe vision impairment or loss.

3.2.1 Pathogen

Toxocara species mainly *T. canis* (dog) and *T. cati/mystax* (cat) are helminths (common ascaris roundworms), which can follow a direct life cycle by infecting definite hosts who shed unembryonated eggs, which become infectious (third-stage larvae, L3) in the environment. Alternatively, they follow indirect life cycles by infecting paratenic hosts where migrating L3 larvae form tissue cysts might finally be inoculated by a definite host. Humans are accidental hosts (L3 larvae cannot complete the life cycle and therefore do not breed eggs) and get infected by accidentally ingesting infectious eggs with contaminated food or water or by consumption of undercooked and raw meat of paratenic hosts containing L3 larvae cysts. After ingestion, L3 larvae penetrate the small intestinal mucosa and circulate via blood to different organs and tissues where the larvae start migrating causing local immunological and inflammatory reactions, which might lead to symptoms. The majority is asymptotically infected. Symptomatic presentations are either visceral or ocular larva migrans. Severity is a function of parasitic load.

3.2.2 Epidemiology

Toxocariasis is worldwide distributed. The majority of ocular larva migrans infections are related to *T. canis* and less frequent reported by *T. cati*/*T. mystax*. Seroprevalence rates for Toxocara antibodies vary from approximately 3 to over 70% [45] with lower rates in industrialized countries and higher rates in low- and middle-income countries related to lower standards in water, sanitation and hygiene and public surveillance, prevention, and control. Exceptions are reported, which mostly are related to habitual food consumption than low hygiene standards [45, 46].

Ocular larva migrans affects children and adults with mean age at onset ranging from 6.4 [47] to 51.7 [48, 49] years and is a significant cause for visual impairment during childhood. The age at presentation with symptoms may vary from 1 to 77 years [48–51].

3.2.3 Clinical peculiarities

Ocular larva migrans is mainly unilateral eye involvement but may appear bilateral [52]. One exclusive feature in ocular larva migrans might be present as migrating granuloma, either continuous or discontinuous. The clinical presentations can be categorized as.

- i. the most common one as posterior pole granuloma. Imposing as posterior pole located whitish, focal intraretinal, or subretinal mass accompanied by inflammation and mostly less than one disc diameter. Pigmentation can be observed as well as vitreous haze and macular lesions [53].
- ii. Peripheral granuloma in the retinal periphery imposing as whitish focal nodule accompanied by diffuse inflammation and sometimes proliferation of fibrocellular bands leading to the optic nerve forming retinal folds, which can cause retinal traction and consecutive retinal detachment.
- iii. Nematode endophthalmitis present as panuveitis, sometimes with hypopyon and more often with vitreous haze and diffuse intraocular inflammation and severe pain [60]. When the inflammation and vitreous haze and vitreous opacity subside, retinal granuloma should be actively searched for.
- iv. Atypical presentations might show motile retinal larvae, diffuse chorioretinitis, optic neuritis [54–56]. Additionally unspecific findings such as iridocyclitis, keratitis, conjunctivitis, or cataract can be found [54].

Vision loss might occur as result to severe intraocular inflammation and consecutive vitritis, aggravation of underlying comorbidities and caused by the location of the granuloma itself.

3.2.4 Diagnostics

Diagnosis can be determined by evaluation of clinical characteristics assessed by basic ophthalmologic methods and supported by imaging via ultrasound and the detection of the typical granuloma in the course. And additionally performed serological tests to detect Toxocara larvae specific serum antibodies via indirect enzyme-linked immunosorbent assay [50, 54, 55]. Titers higher than 1:32 in ELISA indicate

toxocariasis with sensitivity of 78% [57]. In contrast, titers lower than 1:8 cannot completely rule out toxocariasis infection in the presence of typical clinical signs. Total IgE serum levels might support diagnosis and can be beneficial in monitoring treatment efficacy when decreasing under therapy [48, 49]. Eosinophilia as seen in visceral larva migrans is usually not present in ocular larva migrans.

3.2.5 Therapy

Standard treatment of active intraocular inflammation is the application of systemic and topic corticosteroids to reduce inflammation, limiting membrane formation and vitreous opacity, and improving vision [48, 49, 53, 58–60]. Antihelminthic treatment with albendazole or diethylcarbamazine in ocular larva migrans is controversially discussed due to lack of knowledge about intraocular efficacy. The combination with albendazole and corticosteroids shows effects with regard to reduction of recurrence [48, 49, 59] compared with corticosteroid-only treatments. Vitreoretinal surgical interventions might improve vision, if structural problems such as vitreous opacity, retinal detachment, or epiretinal membranes persist after medical therapy [48, 49, 61].

4. Bacterial forms of retinitis

4.1 Tuberculosis

4.1.1 Epidemiology

The WHO reports that more than 2 billion people are affected worldwide by tuberculosis [62]. Extrapulmonary tuberculosis occurs in 20%, and ocular tuberculosis develops from 3.5 to 5.1% of infected people. Patients with HIV often develop a generalization of the specific inflammation process, caused by *Mycobacterium tuberculosis* [63–65].

4.1.2 Clinical features

Ocular tuberculosis has no direct relation to the clinical manifestations of pulmonary tuberculosis; moreover, up to 60% of patients with extrapulmonary variants of tuberculosis do not have affected lungs [66]. According to the results of Collaborative Ocular Tuberculosis Study (COTS) [62, 67], the manifestations of tuberculosis with retinal involvement can be divided into a few different forms:

1. Tubercular posterior uveitis (TPU), the inflammation affects retina and/or the choroid.
2. Tubercular panuveitis (TBP), the inflammation affects anterior chamber, vitreous body and retina/choroid.
3. Tubercular retinal vasculitis (TRV), phlebitis, or arteritis with or without vessel occlusion.

Choroidal tubercles can be characterized as the most common intraocular manifestation of TPU. Choroidal tubercles are disseminated ill-defined, oval, grayish-white or yellowish deep lesions, mostly localized in the posterior pole, they show early hypofluorescence and late staining on fluorescein angiography [68]. Choroidal tubercles may develop itself to choroidal tuberculomas, which present a solitary mass with overlying retinal folds or retinal detachment. These may be located anywhere in the choroid and can be misdiagnosed as intraocular tumors or subretinal abscesses [62].

TRV can be described as perivenular cuffing with thick exudates, with or without retinal hemorrhages, focal choroiditis lesions, and moderate vitritis. Because of occlusive

nature, TRV leads to peripheral capillary nonperfusion and retinal or optic disc neovascularization. These processes can be complicated by vitreous hemorrhage, traction retinal detachment, iris neovascularization, and neovascular glaucoma [68, 69]. These clinical signs are not very specific for a tuberculous etiology; other ocular pathologies, such as sarcoidosis or ocular infection with *Toxoplasma*, can also produce similar clinical forms.

4.1.3 Diagnostics

The interferon- γ release assay (IGRA) indicates a latent or active tuberculosis and quantifies interferon- γ released by sensitized T cells when they were exposed to *M. tuberculosis* peptide antigens. IGRA has some advantages in the diagnostics of the ocular tuberculosis, because it allows to overcome the limitations of tuberculin skin test. The early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) are not present in the Bacille Calmette-Guérin vaccination strains and non-tuberculous mycobacterium species and provide increased specificity of IGRA versus skin tests [70]. There are two available IGRA test systems: the QuantiFERON-TB Gold Plus (QFT-Plus, Qiagen, Hilden, Germany) and the T-SPOT.TB (Oxford Immunotec, Abingdon, UK) [70, 71].

Some clinical particularities need to be considered, before the antitubercular therapy (ATT) is initiated. The usually applied cutoff values (0.35 IU/ml) for QFT were shown to be too low in the setting of uveitis and may lead to overtreatment [72]. A cutoff value of 2.00 IU/ml was proposed instead, based on receiver operating characteristic (ROC) curve analysis, which showed that a threshold of 2.00 IU/ml had 84% sensitivity and 87% specificity for successful ATT in patients with ocular tuberculosis. Moreover, the best option for optimizing the routine screening, based on QFT, is to adjust the cutoff value on local endemicity and epidemiological data [73]. An analysis conducted by Agrawal and colleagues suggests that QFT levels alone cannot adequately separate tuberculosis-positive and -negative patients among patients with clinical signs suggestive of ocular tuberculosis [74]. Thus, if QFT is used as a routine diagnostic tool, its results cannot be taken and interpreted without context. Even negative IGRA test results should be interpreted with caution because they do not exclude the diagnosis.

The nucleic acid amplification enables diagnostics of ocular tuberculosis without the need to detect acid-fast bacilli, which are rarely presented in ocular samples. The quantitative real-time PCR uses fluorescent probes for fast detection and quantification of *M. tuberculosis* load in the sample. The advantage of this procedure is a decreased rate of contamination [75]. Multi-targeted PCR simultaneously amplifies multiple gene targets to achieve a higher diagnostic sensitivity. The sensitivity and specificity of PCR methods were estimated and documented by [71], and sensitivity was ranging from 37.7 to 85.2% and specificity was at a level of 90–100%. The MTBDRplus assay, which was performed on vitreous fluid samples, could detect rifampicin and isoniazid resistance, confirmed by *rpoB* and *katG* gene sequencing [76]. Larger studies must be planned and performed to validate the accuracy and reliability of modern PCR methods [67]. PCR is considered a reliable method, and clinicians should evaluate negative results in correlation with clinical findings, an expected clinical response to ATT supports the PCR results [77].

4.1.4 Therapy

The role of ATT by ocular tuberculosis remains controversial, and there is no international agreement on therapeutic protocols and duration of the ATT [78–82]. Evidence shows efficacy of ATT in reducing the rate of disease recurrences [83].

Results derived from a meta-analysis of 28 studies, which evaluated the effect of ATT on the ocular outcome of 1917 [80] patients, demonstrate that 84% of patients treated with ATT did not experience relapse of inflammation during the follow-up. The role of oral corticosteroids and immunosuppression agents is also still controversial, and there is no agreement on their efficacy in patients with tubercular uveitis treated with ATT [80]. Recent studies show a success of local therapy in the management of tubercular uveitis as an optional adjunctive anti-inflammatory therapy [82, 84, 85].

4.1.5 Prognosis

There is no evidence-based data about long-time prognosis. A low treatment failure rate was shown to occur in patients with tuberculous uveitis treated with ATT. Patients with TBP complicated by vitreous and choroidal involvement had a higher risk of treatment failure [74].

4.2 Ocular syphilis

Syphilis caused by the spirochete bacterium *Treponema pallidum* has an ability to mimic different diseases due to its variety of clinical manifestations.

4.2.1 Epidemiology

The CDC in the United States reported 7.5 cases of primary and secondary syphilis per 100,000 population in 2015; 54% of patients were males, who have practiced sex with other males [86]. The syphilis co-infection of HIV patients ranges from 20% to 70% [87]. Statistical analysis estimates that HIV-positive individuals have an 86 times higher risk of syphilis [63]. Male gender was found to be the only statistically significant risk factor for the development of ocular syphilis; ocular syphilis was seen in 9.5% of men as compared with 1.5% of women [87].

4.2.2 Clinical features

Retinal manifestations of ocular syphilis include following constellations [87]: 1. Chorioretinitis; 2. Necrotizing retinitis; 3. Retinal vasculitis; 4. Retinal vasculitis; 5. Vitritis; 6. Exudative retinal detachment.

Chorioretinitis with vitritis is the most usual finding in syphilitic posterior uveitis and involves the posterior pole and mid-periphery. The inflammatory lesions are initially small, between one-half to one in disc-diameter, but they can become large and confluent [88–90]. The affection of the retina or choroid is usually seen in secondary syphilis, and approximately half of the patients with ocular syphilis experience bilateral involvement [91].

Acute syphilitic posterior placoid chorioretinitis (ASPPC) is a rare manifestation of ocular syphilis [92]. ASPPC is characterized by yellowish, placoid, outer retinal lesions, usually located at or near the macula, with a faded center and stipulation of the retinal pigment epithelium. Such lesions can be seen as the result of active specific inflammation of the chorioretinal complex (choriocapillaris-pigment epithelial-retinal photoreceptor complex). The inflammation can be triggered by dissemination and direct invasion of *T. pallidum*, which causes occlusion of the choriocapillaris or sedimentation of soluble immune complexes, which cause an inflammation of the vessel wall or both of these pathogenetic inflammation ways [92]. Two cases of acute

zonal occult outer retinopathy (AZOOR) were reported in which syphilis was identified as the underlying disease [93]. AZOOR presents with a sudden onset of photopsia and scotoma, which are related to loss of outer retinal sectors function. Fundoscopy can be normal in the early phase of the disease.

Necrotizing retinitis is a seldom complication of ocular syphilis and can mimic acute retinal necrosis [94–96]. Usual clinical features of retinitis associated with ocular syphilis are presented by retinal lesions, which tend to heal with minimal disruption of the retinal pigment epithelium [97]. Vasculitis involves retinal arteries, arterioles, capillaries, and veins [98]. The fundus fluorescein angiography can be complex and demonstrates perivascular exudation and fibrosis, occlusive vasculitis [93, 99], isolated or focal retinal vasculitis, which can simulate branch retinal vein occlusion [100, 101].

4.2.3 Diagnostics

The screening tests used for syphilis diagnostics are enzyme immunoassays (EIA) and chemiluminescent immunoassays (CIA), which detect antibodies to treponemal antigens. If positive, a non-treponemal test, rapid plasma reagin (RPR) or Venereal Diseases Research Laboratory (VDRL) test for cardiolipin antibodies should be performed [87]. The *T. pallidum* hemagglutination assay (TPHA) or *T. pallidum* particle agglutination test (TPPA) detects specific treponemal antibodies. Some of HIV-positive patients can show non-reactive serological results. This phenomenon can be avoided by testing diluted serum [87].

Direct detection can be carried out with dark-field microscopy, PCR, and immune histochemistry. Dark-field microscopy directly visualizes *T. pallidum* by investigation of clinical samples (exudates from chancres, condylomata lata, lymph node aspirates, etc.) [102]. The sensitivity and specificity of dark-field microscopy are approximately 90% and 100%, respectively [103]. PCR of vitreous aspirates can be used, for example, to diagnose atypical manifestations of ocular syphilis [104] and can also be used to identify drug resistance of *T. pallidum* [105, 106].

4.2.4 Therapy

The current CDC guidelines recommend penicillin G as the drug of choice. Primary and secondary syphilis: benzathine penicillin G, 2.4 million units intramuscularly (i.m.) in a single dose. Early latent syphilis: benzathine penicillin G 2.4 million units i.m. in a single dose. Late latent syphilis: benzathine penicillin G 7.2 million units, as three doses of 2.4 million units i.m./week. Tertiary syphilis with normal CSF results: benzathine penicillin G 7.2 million units, as three doses of 2.4 million units i.m./week. Neurosyphilis and ocular syphilis: aqueous crystalline penicillin G 18–24 million units/day, as 3–4 million units i.v. every 4 h or continuous infusion for 10–14 days; or alternatively procaine penicillin G 2.4 million units i.m./days plus probenecid 500 mg orally 4× daily, both for 10–14 days. Systemic steroids have not been proven to have clinical benefits in the treatment of syphilis [107]. All patients with ocular or neurosyphilis should be screened for HIV. Highly effective treatment protocols to prevent neurosyphilis in patients with HIV and syphilis are still not available [108]. However, the antiretroviral therapy can improve clinical outcomes in patients with HIV and syphilis [87].

4.2.5 Prognosis

After serological diagnosis, syphilis treatment is associated with good prognosis [109].

4.3 Ocular manifestations of bartonellosis

There are over 30 different *Bartonella* subspecies. *Bartonella henselae*, *Bartonella quintana*, and *Bartonella bacilliformis* are responsible for most infections in humans. This organism is a Gram-negative hematotropic pathogen, it affects erythrocytes and/or endothelial cells. The clinical form can manifest as disseminated vascular proliferations throughout the body [110].

4.3.1 Epidemiology

Cats are the main reservoir, and over 90% of patients with *Bartonella* species infection have had a contact with a cat [111]. The clinical infection with *Bartonella* species has the term Cat-scratch disease (CSD) as a synonym. A multicenter retrospective study of CSD patients with ocular manifestations was performed between 1996 and 2015 [112]. Seasonal patterns were observed with ocular CSD [112]. Ocular bartonellosis has a broad age distribution [113]. In one clinical study, 141 of 3222 patients (4.4%) have had concomitant ocular manifestation of CSD [114].

4.3.2 Clinical features

The posterior segment manifestations of CSD include intermediate uveitis, optic neuritis, neuroretinitis, focal or multifocal retinitis and/or choroiditis, vascular occlusions, retinal vasculitis, granulomas, exudative retinal detachments, macular exudates, macular hole, white dot syndromes, angiomatous lesions, and acute endophthalmitis [115–117]. Patients may experience a varying severity of unilateral or bilateral visual loss and central scotoma. Neuroretinitis presents as optic disc swelling with serous retinal detachment, and macular exudation, which can be seen 2–4 weeks after the initial observation of optic disc swelling. The macular exudates can take a long time to resolve, up to 12 months [112].

4.3.3 Diagnostics

The diagnosis of CDS is based on the presence of the following clinical criteria [114]: 1. Contact with cats; 2. Positive skin test in response to CSD antigen; 3. Characteristic lymph nodes and lymphadenopathy not caused by other bacteria.

The best screening test for diagnostics of CSD is a serologic testing by either indirect fluorescence assay (IFA) or ELISA [118]. The IFA test has a sensitivity and specificity of 90% in immunocompetent patients and is the more commonly used diagnostic test [115, 119]. PCR is also a useful diagnostic test in particular by negative serology. PCR demonstrates a high specificity, but the sensitivity is lower than serology testing [119].

4.3.4 Therapy

Antibacterial therapy can be performed with the following antimicrobial drugs: doxycycline, macrolide antibiotics (clarithromycin, erythromycin, azithromycin), rifampicin, ciprofloxacin, ceftriaxone, and cotrimoxazole [111]. The usual therapy includes doxycycline 100 mg 2× per day for 4–6 weeks for immunocompetent patients and up to 4 months for immunocompromised patients. Younger patients can be treated with a macrolide antibiotic because of less long-term side effects [119].

Corticosteroids may be used as additional therapy component to antibiotic treatment with the aim to stop and control the inflammatory response. A multivariate logistic regression analysis has shown a significant improvement of visual acuity by a combination therapy (systemic corticosteroids and antibiotics) [112].

4.3.5 Prognosis

Most patients reached a good final visual acuity [112].

5. Conclusions

Several viral, parasitic, and bacterial pathogens form the major causes for infectious retinitis. Since the phenotype is not absolutely specific for the individual infection, specific diagnostic procedures focusing on the major pathogens and, in most cases, on nucleic acid amplification need to be used. Due to the individual pathogen, specific therapy is possible in many cases and increases the quality of the therapeutic outcome. Nevertheless, the current therapeutic results demand further development and improvement of the therapy of infectious retinitis.

Author details

Ruben Rose, Alexey Gorin, Mathias Voß and Helmut Fickenscher*
Institute for Infection Medicine, University Medical Center Schleswig-Holstein,
Christian-Albrecht University of Kiel, Kiel, Germany

*Address all correspondence to: fickenscher@infmed.uni-kiel.de

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