NIH Public Access
Author Manuscript
Clin Experiment Ophthalmol. Author manuscript; available in PMC 2014 May 21.

Published in final edited form as:
Clin Experiment Ophthalmol. 2013 ; 41(1): 95–108. doi:10.1111/j.1442-9071.2012.02838.x.

Ocular toxoplasmosis II: clinical features, pathology and management

Nicholas J Butler, MD[1], **João M Furtado, MD, PhD**[2], **Kevin L Winthrop, MD, MPH**[2,3,4], and **Justine R Smith, MBBS, PhD**[2,5]

[1]Division of Ocular Immunology, Wilmer Eye Institute, Johns Hopkins School of Medicine, Baltimore, Maryland [2]Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, USA [3]Department of Medicine, Oregon Health & Science University, Portland, Oregon, USA [4]Department of Public Health, Oregon Health & Science University, Portland, Oregon, USA [5]Department of Cell & Developmental Biology, Oregon Health & Science University, Portland, Oregon, USA

Abstract

The term, ocular toxoplasmosis, refers to eye disease related to infection with the parasite, *Toxoplasma gondii*. Recurrent posterior uveitis is the typical form of this disease, characterized by unilateral, necrotizing retinitis with secondary choroiditis, occurring adjacent to a pigmented retinochoroidal scar and associated with retinal vasculitis and vitritis. Multiple atypical presentations are also described, and severe inflammation is observed in immunocompromised patients. Histopathological correlations demonstrate focal coagulative retinal necrosis, and early in the course of the disease, this inflammation is based in the inner retina. For typical ocular toxoplasmosis, a diagnosis is easily made on clinical examination. In atypical cases, ocular fluid testing to detect parasite DNA by polymerase chain reaction or to determine intraocular production of specific antibody may be extremely helpful for establishing aetiology. Given the high seroprevalence of toxoplasmosis in most communities, serological testing for *T. gondii* antibodies is generally not useful. Despite a lack of published evidence for effectiveness of current therapies, most ophthalmologists elect to treat patients with ocular toxoplasmosis that reduces or threatens to impact vision. Classic therapy consists of oral pyrimethamine and sulfadiazine, plus systemic corticosteroid. Substantial toxicity of this drug combination has spurred interest in alternative antimicrobials, as well as local forms of drug delivery. At this time, however, no therapeutic approach is curative of ocular toxoplasmosis.

Keywords

ocular toxoplasmosis; uveitis; clinical; pathology; diagnosis; treatment

© 2012 The Authors Clinical and Experimental Ophthalmology © 2012 Royal Australian and New Zealand College of Ophthalmologists

Correspondence: Prof. Justine R Smith, Casey Eye Institute, 3375 SW Terwilliger Blvd, Portland, OR 97239, USA. smithjus@ohsu.edu.

Competing/conflicts of interest: No stated conflict of interest.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Introduction

Since the 1950s, toxoplasmosis has been recognized as a form of inflammatory eye disease that follows intraocular infection with the parasite, *T. gondii*.[1] Today, toxoplasmic retinochoroiditis or 'ocular toxoplasmosis' is one of the most common causes of posterior uveitis worldwide, although the risk of infection and subsequent ocular involvement vary in different parts of the world.* In this review, we describe the clinical features and course of ocular toxoplasmosis, as well as histopathological observations. We also describe current approaches to the diagnosis and treatment of this infectious disease.

Clinical manifestations of ocular toxoplasmosis

The clinical manifestations of ocular toxoplasmosis have been definitively discussed by Holland *et al.* in the text, *Ocular Infection and Immunity*[2] and the publication of Dr. Holland's LX Edward Jackson Memorial Lecture.[3] Ocular toxoplasmosis may be asymptomatic in young children. Children who are able to vocalize may complain of decreased vision or ocular pain, while parents may note leukocoria or strabismus. Adults often present with floaters, which may be associated with altered vision. The 'classic' sign of infection, that is, a nidus of fluffy white, necrotizing retinitis or retinochoroiditis adjacent to a variably pigmented chorioretinal scar, is routinely seen. Descriptions of atypical manifestations abound, but these cases are assumed to represent essentially the same disease with regard to pathogenesis and management.[3] The focus of retinitis is usually full thickness, although limited involvement of either inner or outer retina, as originally described by Friedmann and Knox,[4] may also be encountered. Depending upon the size and thickness of involved retina, the overlying vitreous and subjacent choroid are variably involved. Large, full-thickness lesions tend to incite a more severe vitritis, producing the classic 'headlight in the fog' sign.[2] Spontaneous resolution of active retinochoroiditis, with or without treatment, is expected within 1 to 2 months in immunocompetent persons, while remission without treatment would be exceptional in individuals with acquired immunodeficiency syndrome (AIDS).[2] An atrophic, well-defined retinal scar results. This scar is often smaller than the initially involved area of retina, and variable pigmentation and choroidal atrophy may relate to the degree of retinal pigment epithelial damage during the active phase.[3]

Ocular toxoplasmosis commonly manifests in the second through fourth decades.[4,5] In reviewing a large series of 154 patients with active toxoplasmic retinitis, Bosch-Driessen *et al.*[5] found the mean age at first presentation for symptomatic infection to be 29.5 years. The exact age of onset was difficult to ascertain, however, as 72% of these patients were discovered to have pre-existing retinochoroidal scars, indicating prior subclinical disease. The authors of this detailed report observed that patients presenting with active ocular toxoplasmosis in the chronic phase of systemic infection, based on serology, were significantly younger than those presenting with eye disease during the acute phase of infection (i.e. 29.9 years *vs.* 50.6 years). This finding, which had been previously reported for smaller cohorts,[6,7] was considered to reflect declining cell-mediated immunity with age.[5]

*Furtado *et al.*, Ocular toxoplasmosis I: parasitology, epidemiology and public health. Clin Experiment Ophthalmol (in press).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In the overwhelming majority of immunocompetent hosts (i.e. 72%–83%), ocular toxoplasmosis is unilateral, whether occurring as primary or reactivated disease.[8] The parasite has a poorly understood proclivity for the posterior pole, affecting this part of the retina in greater than 50% of cases.[3,5,8] In contrast to infection in immunocompromised patients, in the healthy adult, virtually all cases of active ocular toxoplasmosis presents as a single focus of retinitis, even in the setting of multiple retinochoroidal scars.[3]

In addition to retinitis or retinochoroiditis, a host of other clinical findings are observed in patients with ocular toxoplasmosis. Vitritis is usually a prominent feature, and may range from scant to severe.[9] Extramacular lesions, older age and increasing lesion size have all been associated with higher vitreous cell and/or haze scores.[9] When present, retinal vasculitis more often involves the local venous vasculature; however, retinal arteries may be involved, and vasculitis may also occur remote from the active lesion.[10] An arteriolitis with segmental intravascular yellow-white *Kyrieleis* plaques may be observed.[11] Granulomatous or non-granulomatous anterior uveitis occurs, often indicating relatively severe vitritis and frequently associated with elevated intraocular pressure.[9,12] Older age has been correlated with granulomatous anterior uveitis.[5] Whether the result of direct parasitic invasion or reactive inflammation, optic nerve involvement may occasionally be seen.[13–16] Eckert *et al.*[15] reviewed the records of 926 patients with toxoplasmic retinitis and identified optic nerve changes in 5% of these individuals. In 43% of cases, the retinitis was distant from the optic nerve, and in 35%, it was juxtapapillary. Interestingly, others have found an increased risk of the juxtapapillary location in the chronic phase of systemic infection compared to the acute (i.e. 21% *vs.* 0%).[5] ‘Pure papillitis’, which was defined as a swollen optic nerve head with sheathed peripapillary veins and healed retinochoroiditis, was observed by Eckert *et al.*[15] in just three of the 51 cases involving the optic nerve. Patients with optic nerve involvements tend to be younger and healthy, and despite the dramatic presentation, their vision often improves substantially.[15] In contrast, when toxoplasmic optic nerve disease occurs in patients with AIDS, the prognosis is poor.[17]

Although infrequently encountered, numerous case reports of atypical manifestations of ocular toxoplasmosis are found in the medical literature. Such cases are often diagnostically challenging. Punctate outer retinal toxoplasmosis is characterized by clusters of gray-white lesions measuring 25 μm to 75 μm in diameter that resolve slowly and induce little vitritis. This entity usually presents in younger, immunocompetent patients[4,18–20] but has been reported in an HIV-positive child.[21] Macular involvement and severe disc oedema are common. Interestingly, the lesions appear bilaterally in one third of patients.[8] Potentially associated with newly acquired systemic infection,[3] neuroretinitis is another reported atypical presentation of ocular toxoplasmosis.[22,23] In their review of 51 cases of toxoplasmic optic neuropathy, Eckert *et al.*[15] found no cases of neuroretinitis, suggesting that occurrence is a rare event. However, this finding warrants a search for recently acquired systemic infection and/or signs of active or resolved retinitis consistent with toxoplasmosis.[3] Aggressive therapy is advocated,[8] and despite marked initial reduction in visual acuity, substantial improvement has been reported.[22,23] Like typical disease, toxoplasmic neuroretinitis may be recurrent.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Many other atypical presentations of ocular toxoplasmosis have been described[11] including: pseudo-multiple retinochoroiditis;[8] Coats-like retinopathy;[24] pigmentary retinopathy;[25] retinal vascular occlusion;[26,27] Roth spots;[28] serous retinal detachment;[29] optic disc granuloma;[14] scleritis;[30] and anterior, intermediate, anterior/intermediate, posterior and pan-uveitis in the absence of overt retinitis.[8,31,32] Holland *et al.*[31] postulate that intraocular inflammation in the absence of retinitis may be an initial ophthalmic manifestation of recently acquired *T. gondii* infection, as some affected individuals eventually develop toxoplasmic retinochoroiditis in the same eyes. There has been debate in the literature regarding a potential association between toxoplasmic retinochoroiditis and Fuchs' heterochromic iridocyclitis,[33–36] and current opinion does not support a causal relationship between these diseases.[37]

In contrast to the atypical presentations of ocular toxoplasmosis, which are not necessarily more severe than typical retinochoroiditis, ocular toxoplasmosis in immunocompromised individuals frequently demonstrates a relatively fulminant course.[6,38–46] The situation is well exemplified by two cases of disease occurring in patients with AIDS that were reported by Moorthy *et al.*;[44] in these unfortunate individuals, toxoplasmic retinochoroiditis progressed to panophthalmitis and orbital cellulitis, and resulted in loss of light perception, despite treatment. Patients with AIDS are particularly susceptible to acute and reactive infections with *Toxoplasma gondii*, particularly when CD4-positive T cells are reduced below 250 cells/mm^2.[47] Other groups at risk of severe ocular inflammation include elderly persons, patients on treatment with locally injected or systemically administered corticosteroid and patients taking systemic immunosuppressive therapy. Potential presentations include multifocal disease in one eye, bilaterally active inflammation and/or extensive areas of necrotizing retinitis. Diagnostic confusion with viral retinitis may necessitate intraocular fluid analysis.[48,49] However, clinical features, including the lack of retinal haemorrhages, and discrete, smooth-contoured edges to the lesion, are helpful in distinguishing a toxoplasmic aetiology.[50]

The location of toxoplasmic lesions within the retina was discussed by Dr. Holland in his LX Edward Jackson Memorial Lecture:[3] macular lesions are more common than would be expected if distribution across the retina occurred randomly, and Dr. Holland suggested that this might reflect regional anatomical differences, including variations in the microvasculature and the distribution of immune cells. Interestingly, Bosch-Driessen *et al.*[5] found a significantly increased likelihood of macular lesions (i.e. 46% and 16%), as well as bilateral disease (i.e. 85% and 28%), in congenital *versus* postnatal infections, respectively. Mets *et al.*[51] reported macular involvement in 55% and bilateral involvement in 51% of 94 patients with confirmed congenital ocular toxoplasmosis. Congenital infections are not necessarily more severe than postnatal cases,[3] but given the higher incidence of macula involvement, congenital infection carries an increased risk of legal blindness.[5,52]

As discussed elegantly by Holland,[3] the wide variations that are observed in the severity of toxoplasmic retinochoroiditis reflect a complex interplay between host immune defences, parasite virulence and environmental factors. Severe inflammation is likely to result in ocular complications and poor visual outcome. Reported complications of ocular toxoplasmosis include isolated retinal tear (6%), retinal detachment, which is usually

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

rhegmatogenous and/or tractional (6%), retinal vascular occlusion (5%), pre-retinal membrane (7%), macular oedema (12%), choroidal neovascularization (<1%), vitreous haemorrhage (2%), optic atrophy (4%), cataract (5%–13%) and raised intraocular pressure (30%–38%).[5,9,10,12,53–55] Retinal vascular occlusion is most commonly encountered when a retinal vessel passes directly through an area of active retinitis.[10,55] Posterior and anterior synechiae, and iris atrophy are unusual complications that may be more common among Brazilians.[9] In their review of 154 patients with ocular toxoplasmosis, Bosch-Driessen *et al.*[5] found that 44% developed complications, and 18% required at least one intraocular surgery. These researchers additionally noted a relatively increased risk of complications in patients presenting during an acute systemic infection, and this subset of individuals also had a higher risk of progressing to legal blindness. Overall, 24% of patients developed legal blindness in one eye, generally from retinitis and subsequent scarring within the macula, retinal detachment or optic atrophy.

Recurrences of active retinochoroiditis have been reported to occur in 79% of 76 patients followed for over 5 years.[5] Infection appears to recur with increased incidence from the same location along the scar border.[3] Pregnancy and cataract surgery have both been associated with an increased risk of reactivation.[3,54] Recently, Holland *et al.*[56] reported an unadjusted rate of recurrence of 0.2 episodes/year in a cohort of 143 Dutch patients followed for up to 41 years. They noted the recurrence risk decreased with increasing disease-free interval (i.e. 72% relative risk reduction with each disease-free decade) and increasing age at first clinical episode. Late recurrences demonstrated clustering in time, as opposed to a random distribution. The observation that patients who are relatively young at first presentation are at increased risk of recurrence compared to older patients has been independently confirmed;[57] and a larger retinal parasite load in younger patients is one explanation that Holland *et al.* offer for this observation.[56] In patients with AIDS and reduced CD4-positive T cell count, recurrence is the rule in the absence of long-term anti-parasitic therapy.[58] The risk of reactivation in patients with inactive toxoplasmic retinal scars who receive treatment with systemic corticosteroid for other indications is probably very low. Concurrent treatment directed against *T. gondii* is not recommended as a routine, although it may be considered in persons who have suffered recurrent disease and who are at high risk of irreversible vision loss on further recurrence.[59] Immunocompromised persons are also more prone to the ocular toxoplasmosis. Research conducted at San Francisco General Hospital calculated a relative incidence risk ratio of 2.1:1 for HIV-positive *versus* HIV-negative patients.[60]

Systemic manifestations of infection with *T. gondii* differ considerably for infections transmitted *in utero versus* those acquired later in life. Congenital toxoplasmosis develops in 30% to 50% of infants whose mothers are first infected during pregnancy, and 70% to 90% of affected infants develop retinochoroiditis.[2] The risk of congenital toxoplasmosis is highest in the third trimester (i.e. 72% at 36 weeks *versus* 6% at 13 weeks gestation),[61] but systemic manifestations are most severe if the infection is contracted during the first trimester. Spontaneous abortion may occur, or the child may be born with abnormalities that include hydrocephaly, microcephaly, intracranial calcifications, epilepsy, psychomotor retardation and leukopenia.[62] It is generally accepted that there is no significant risk of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

infecting the unborn child if the mother acquires disease before pregnancy; however, the case of a woman with a 20-year history of ocular toxoplasmosis who delivered a boy with congenital toxoplasmosis indicates the possibility.[63] Similarly, foetal infection during a reactivation of ocular toxoplasmosis in the mother is rare due to the protective maternal immune response. These transmissions have been linked to an immunocompromised state of the mother, relating to conditions such as AIDS or systemic immunosuppressive therapy.[64]

Immunocompetent persons who acquire ocular toxoplasmosis after birth usually do not have systemic symptoms, although asymptomatic cervical lymphadenopathy is common.[62] Approximately 10% of otherwise healthy individuals who contract the infection report non-specific symptoms, such as fatigue, fever and myalgias.[62] In contrast, a high incidence of symptomatic systemic disease (i.e. 94%) has been reported in the context of epidemic infection.[65] Infection in patients who are immunocompromised most commonly presents as encephalitis and may be fatal.[62] Thus, the 1-year incidence of clinical toxoplasmic encephalitis in HIV-positive patients with CD4-positive T cell counts under 100 cells/mm^2 and positive *T. gondii* serology is approximately 25%, and only 30% survive 1 year after the diagnosis of toxoplasmic encephalitis.[66] Pneumonitis or septic shock are other systemic manifestations of toxoplasmosis that occur in immunocompromised hosts.[62]

Pathological Observations In Eyes Infected With *T. Gondii*

The literature contains multiple publications of histopathological and ultrastructural observations made on ocular biopsy specimens or whole globes taken from individuals with ocular toxoplasmosis or human cadavers with pre-morbid infection.[1,17,39–41,43,67–72] However, there is a paucity of information regarding pathological changes in otherwise healthy adults who constitute the largest group of patients presenting for ophthalmic care of this condition. Most reports describe disease in foetuses or infants,[68,69] or adults who were predisposed to severe infection due to pharmacologically induced immunodeficiency,[39–41] AIDS[17,43,70] and elderly age group.[71] Not unexpectedly, these reports present cases of aggressive infections, and descriptions of ocular changes in adult human eyes during the initial stages of disease are missing from the literature.

In 1951, Hogan[67] presented a summary of the histopathological changes found in eyes at autopsy of 13 infants diagnosed with congenital toxoplasmosis. Almost simultaneously, in 1952, Wilder[1] published her findings in 53 eyes from patients aged 14 to 83 years, who presented with chorioretinal lesions and in most cases lacked a history suggestive of systemic infection. The majority of these eyes were previously diagnosed as ocular tuberculosis, but they contained ‘organisms morphologically indistinguishable from *T.gondii*’. This report was the first description of ocular toxoplasmosis in adults. Both reports described key histopathological changes that were subsequently summarized by Zimmerman[73] in his review of the ocular pathology of toxoplasmosis, which appeared in *Survey of Ophthalmology* in 1961. In particular, the disease is characterized by focal coagulative retinal necrosis and granulomatous inflammation of the choroid adjacent to the affected retina.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Two studies of foetal eyes that were infected *in utero* with *T. gondii* provide a picture of the early stages of congenital ocular toxoplasmosis. Brézin *et al.*[69] reported histopathological findings in three eyes of two foetuses from pregnancies terminated at 22 and 25 weeks, respectively. These eyes showed multiple areas of extensive retinal necrosis, with leukocytic infiltration of necrotic and adjacent retina, as well as choroid. Disruption of retinal pigment epithelium (RPE) was associated with an accumulation of pigment granules in necrotic areas. Roberts *et al.*[68] described their findings in 15 eyes from 10 foetuses aborted between 19 and 32 weeks' gestation. A majority of eyes demonstrated focal retinal necrosis with disruption of the RPE and a chronic inflammatory infiltrate of the underlying choroid, as noted in the previous report. In some eyes, including those without retinal lesions, chronic inflammation of iris and ciliary body was also observed. By immunohistochemistry, infiltrating leukocytes were characterized as T and B lymphocytes, plasma cells and macrophages; T cells predominated over B cells, and the majority of T cells were CD4 positive. Interestingly, leukocytes were rare in eyes of the 32-week-gestation foetus as well as eyes of a 2-year-old child that were also examined, presumably representing a later stage in the disease. Focal retinal dysplasia, with formation of Flexner-Wintersteiner rosettes, in the older foetus was attributed to ‘insult … prior to organization of the retinal layers’.[68] Other histo-pathological findings in some cases were retinal gliosis, retinal neovascularization, retinal detachment and optic neuritis.

At least five eyes of patients with ocular toxoplasmosis and AIDS, all of whom were treated during the 1980s and rapidly succumbed to infection, have been described microscopically.[17,43,70] Full thickness retinal necrosis, with underlying disruption of the RPE and choroiditis, were features common to these eyes. In several cases, it was noted that the necrotic retina did not appear inflamed, but choroidal infiltration was heavy, and infiltrating leukocytes included lymphocytes, plasma cells, histiocytes and eosinophils. Pigment-laden macrophages were also identified in some eyes. Other microscopic findings included inflammatory infiltration of the anterior segment and vitreous, retinal vascular thrombi, retinal haemorrhage, exudative detachment of the neuroretina or RPE, proliferation of the RPE and optic nerve inflammation.

Additional published histopathological observations in adult cases of ocular toxoplasmosis include one patient with presumed sarcoidosis, treated with long-term systemic corticosteroid, who died suddenly within a year of developing bilateral retinitis.[39] The pathology in this case was relatively less advanced than that observed in the patients with AIDS. Most retinal necrosis involved only the nerve fibre and ganglion cell layers, adjacent to retinal arteries and veins. There was no intraretinal inflammation, but a chronic non-granulomatous chronic inflammatory infiltrate was present in ciliary body and vitreous and in choroid adjacent to areas of neuroretina and RPE that exhibited full thickness necrosis. Similar findings of inner retinal necrosis without inflammation, and non-granulomatous choroiditis and vitritis were described for one eye of a patient with ocular toxoplasmosis following chemotherapy for lymphoma.[40] Electron microscopic observations in this case included multi-laminar placoid proliferation of the RPE, and glial proliferation within and on the surface of necrotic retina. One eye of an elderly male with 6-year history of ocular toxoplasmosis demonstrated necrosis of the entire neuroretina and portions of RPE, with

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

diffuse granulomatous choroiditis and a heavy heterogeneous leukocytic infiltration of vitreous and anterior segment structures.[71] In a separate histopathological study of the eye from a patient who developed ocular toxoplasmosis following liver transplantation, extensive retinal necrosis was associated with retinal arteriolar occlusive thrombi, disruption of RPE, granulomatous choroiditis, vitritis and optic neuritis.[41]

T. gondii parasites were detected in bradyzoite and/or tachyzoite form in the aforementioned pathological studies of foetal eyes and eyes from individuals with AIDS or other immunocompromised states.[17,39–41,43,68–71] Most commonly, organisms were identified by haematoxylin and eosin or other standard histopathological stains. However, other techniques with greater sensitivity for the organisms were also used, including immunohistochemistry, electron microscopy and polymerase chain reaction (PCR) detection of the *T. gondii* B1 gene. For immunohistochemistry, antibodies specific for *T. gondii* antigens are now commercially available. In the different studies, parasites were observed in both healthy and necrotic retina, but were most commonly seen in areas of necrosis or immediately adjacent to these areas. In some cases, parasites were also detected within inflamed optic nerve. Two groups reported the presence of parasites in close vicinity to blood vessels, consistent with spread from the vascular tree to the retina,[43,68] and a separate study of an eye from a patient with AIDS indicated localization of tachyzoites to the inner retina.[70]

Diagnosis of Ocular Toxoplasmosis

The diagnosis in the majority of cases of ocular toxoplasmosis is made on distinctive clinical findings, that is, an area of active necrotizing retinochoroiditis at the edge of a pigmented chorioretinal scar. However, in atypical cases or fulminant expressions of disease, with retinitis mimicking other infectious and non-infectious entities or obscured by dense vitritis, or when there is delayed response to treatment, analysis of an intraocular fluid specimen may be extremely helpful in identifying *T. gondii* as the causative organism. Indeed, two independent groups have shown that results of ocular fluid testing favourably impact the clinical course in approximately 25% of patients with apparent infectious posterior uveitis.[74,75]

As explained in the comprehensive review by Van Gelder,[76] the PCR is a highly sensitive and specific method that has found important application in the specific diagnosis of infectious uveitis. Limitations of this test include potential for false-positives related to contaminating DNA in reagents and equipment, or DNA from commensals or non-viable organisms, and for false-negatives if primer design is flawed, or sample or reagents are degraded. When used to diagnose ocular toxoplasmosis, PCR most commonly involves the amplification of the toxoplasmic B1 gene, which is replicated 35-fold within the parasite's genome, but absent from mammalian cells. Although generally less sensitive for diagnosis of *T. gondii* in ocular fluids than herpes viruses, a rate of up to 67%[74] certainly exceeds yields by culture or cytology. Moreover, the procedure is not laborious, and results are potentially available within the day. Amplification of other multiple repeat sequences within the genome of *T. gondii* is being studied as a way to improve the sensitivity of testing.[77] The value of PCR analysis is quickly realized in one early report of the detection of toxoplasmic

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

DNA from a retinal lesion that could not be diagnosed by histo-pathologic review of the affected whole eye.[78]

In reviewing a large series of 133 patients with suspected infectious uveitis affecting the posterior segment of the eye, Harper *et al.*[74] found PCR of ocular fluid to have an overall sensitivity and specificity of 80.9% and 97.4%, respectively, using final clinical diagnosis as the gold standard. For *T. gondii* in particular, the sensitivity was 67%, which was lower than the 82% to 100% recorded for different herpes viruses. Positive results occurred with similar frequency whether aqueous or vitreous were tested. However, and as the authors highlighted, since few cases involved both aqueous and vitreous sampling, it was not possible to draw specific conclusions, including relative sensitivity for detection of *T. gondii* in different ocular fluids. As discussed by Montoya *et al.*[79] who performed PCR on vitreous to diagnose 15 patients with atypical features, vitreous testing by PCR may be more sensitive for ocular toxoplasmosis in particular. On the other hand, sampling aqueous poses relatively less risk to the eye.

Several reports from the University Medical Center Utrecht have compared PCR and measurement of specific intraocular antibody in aqueous humour for the diagnosis of infectious uveitis syndromes, including toxoplasmic retinochoroiditis.[75,80,81] The Goldmann-Witmer coefficient (GWC) is calculated as the proportion of specific immunoglobulin (Ig)G in ocular fluid *versus* serum samples. Although a ratio over one should indicate intraocular antibody production, this also occurs in healthy controls, and therefore a ratio of at least three is often preferred for certain diagnosis.[82] In 2006, the group described aqueous humour testing for ocular pathogens in 230 immunocompetent persons with suspected infectious uveitis.[81] For the 25 patients who suffered from ocular toxoplasmosis, the GWC was positive in 90%, while PCR testing was positive in just 36%. This study highlighted the importance of the time point at which the aqueous is sampled; although the GWC was positive throughout the first 3 months after disease onset, PCR first became detectable at 3 weeks. The following year, the investigators reported a similar study conducted in 56 immunocompromised patients; for the 10 patients with ocular toxoplasmosis by testing, the GWC was positive in 90%, and PCR testing was positive in 40%.[80] In the subsequent study of 152 immunocompetent and immunocompromised patients with posterior uveitis, the group again identified the value of the GWC in the diagnosis of ocular toxoplasmosis; PCR detection of the pathogen was significantly more likely in viral *versus* toxoplasmic infections.[75]

Lower rates for PCR detection of *T. gondii* in the studies from The Netherlands[75,80,81] compared to that reported by Harper *et al.*[74] might reflect differences in specific immune status of the study subjects and/or the severity of the ocular infections, although these factors were not determined for individual pathogens. Several studies support this speculation. Fardeau *et al.*[83] reported a similarly higher yield for GWC (48%) *versus* PCR (16%) on aqueous from 56 patients with a clinical diagnosis of atypical toxoplasmosis. However, all nine PCR-positive cases occurred in persons who were either elderly or immunocompromised as a result of illness, and all were characterized by extensive retinitis, averaging nearly 12 disc areas. Interestingly and in contrast, the GWC was elevated in only two of these nine cases. A report from the same group included nine immunocompromised

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

patients with a presentation consistent with acute retinal necrosis, caused by *T. gondii*.[48] Aqueous from this group was positive for *T. gondii* by PCR in eight cases and by GWC in two cases. In a population of 27 persons aged over 50 years, Labette *et al.* noted the aqueous PCR was positive in 60% when lesions were larger than three disc areas but in 25% when lesions were smaller. Overall, GWC was more likely positive than PCR (i.e. 89% *vs.* 44%) in this group, however.

Several groups have commented on the complementary nature of PCR and GWC testing.[46,81,83] Researchers from France have described the use of immunoblotting to further improve the sensitivity of laboratory testing for *T. gondii* in ocular fluids. By this method, a Western blot is performed using patient serum to probe a membrane containing electrophoretically separated *T. gondii* antigens. In two independent studies, combining PCR analysis, the GWC and an immunoblot to analyze aqueous samples resulted in sensitivities for diagnosis of ocular toxoplasmosis of 83%[84] and 97%.[85] Although tests for detection of anti-*T. gondii* antibody in intraocular fluid is widely performed throughout Western Europe, such testing is not routinely available in many other countries, where PCR is the standard method for examining ocular fluid.

Serological testing for *T. gondii* plays little role in the diagnosis of ocular toxoplasmosis. Its primary use is in the exclusion of ocular toxoplasmosis as the cause of posterior uveitis if specific antibody is absent from the serum. Within 1 to 2 weeks of an infection, (Ig) G directed against *T. gondii* appears in the serum and will remain detectable for the lifetime of the patient.[68] Since seropositivity is prevalent in most communities, the positive predictive value of IgG is low, and a positive IgG cannot be interpreted as indicative of active toxoplasmic infection. A rise in titre of specific IgG antibodies over a 3-week period has been used as an indicator of recent infection, however.[86] If retinitis develops within a year of an acquired systemic infection, anti-*T. gondii* IgM should also be detectable, but the variable rate of decline of this Ig isotype also limits the usefulness of such testing. The only exception is during pregnancy, when maternal IgM may herald acute infection of both mother and foetus, and should trigger urgent consultation with the obstetrician and neonatologist.[64] Tests for specific IgA and IgE have similar limitations, and are not widely employed.[62]

Medical Treatment of Ocular Toxoplasmosis

In the immunocompetent individual, toxoplasmic retinochoroiditis typically resolves over a period of 1 to 2 months.[2] Given this benign natural history and the potential toxicity of anti-parasitic medication, treatment of all comers with active infection would result in an unnecessarily high rate of drug-related morbidity. Therefore, a clinical analysis of the risks and benefits of therapy is generally performed on a case-by-case basis. Since no drug has been shown to cure infection in the human host, the goal of antimicrobial treatment continues to be limiting parasite multiplication during active retinitis.[87] In reviewing the medical literature in 2003, Stanford *et al.*[88] drew attention to the lack of evidence for effectiveness of treatment for acute toxoplasmic retinochoroiditis. Of 152 studies screened, they identified just three randomized controlled clinical trials, all of which were described as ‘methodologically poor,’ and none of which reported permanent visual outcome. No

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

additional randomized placebo-controlled trials have been published since that review. Despite this situation, a majority of ophthalmologists treat immuno-competent patients with active inflammation who have: reduced visual acuity; lesion located within the temporal arcades or adjacent to the optic disc; and/or vitreous haze above grade 1+.[89] Atypical presentations and disease in immunocompromised patients are widely considered an indication for treatment.[11] Members of the American Uveitis Society (AUS) were questioned about their preferred treatment strategies for ocular toxoplasmosis in 1991[90] and again in 2001.[89] Comparison of results of the two surveys revealed a notable shift in management attitudes over time, in favour of treatment of both mild and severe disease.[89]

The terms, ‘classic therapy’ or ‘triple-drug therapy’ in relation to ocular toxoplasmosis, refer to the combination of pyrimethamine (25 mg–50 mg daily orally in one to two doses),[89] sulfadiazine (1 g four times daily orally)[89] and systemic corticosteroid (often in the form of prednisone). Pyrimethamine and sulfadiazine have been combined to treat ocular toxoplasmosis since the 1950s.[91] They act at different steps in the synthesis of tetrahydrofolate, and thereby impact nucleic acid synthesis by *T. gondii*. Pyrimethamine inhibits dihydrofolic acid reductase, and sulfadiazine is a competitive antagonist of *p*-aminobenzoic acid. Rothova *et al*.[87] studied 149 consecutive patients presenting to six academic centres in The Netherlands in the largest prospective trial assessing treatment effectiveness of antimicrobial treatment in ocular toxoplasmosis in a non-AIDS population. They reported that duration of retinitis at the posterior pole was not significantly shortened by any one of three therapies – classic therapy; the combination of clindamycin, sulfadiazine and systemic corticosteroid; and the combination of trimethoprim, sulfamethoxazole and corticosteroid – in comparison to peripheral retinitis in untreated control subjects. Rates of recurrence were also not influenced by treatment. They did find, however, that patients treated with classic therapy showed a greater reduction in the size of the retinal lesion than patients receiving other treatments or no treatment, and this difference was statistically significant for the comparison with the untreated group. Hence, the authors concluded that classic therapy may be appropriate for lesions involving or adjacent to the fovea, where size is critical to visual outcome.

Both in 1991 and in 2001, just one third of AUS members selected classic therapy as their preferred approach to ocular toxoplasmosis.[89,90] Apart from the lack of evidence for therapeutic benefit, concern about drug-related toxicity also contributes to the relatively low popularity of this treatment regimen. Indeed, in the study by Rothova *et al.*,[87] 26% of patients treated with triple therapy discontinued treatment due to complications. Pyrimethamine may cause gastrointestinal and dermatological side effects, but the most concerning adverse events are haematological, including leukopenia and thrombocytopenia. For this reason, weekly monitoring of blood cells should be continued throughout the course of treatment. In addition, patients are prescribed folinic acid (5 mg every other day orally),[89] which is a reduced form of folic acid that cannot be metabolized by *T. gondii*. Interestingly, in one treatment study, Rothova's clinical team administered folinic acid to 46 patients treated with pyrimethamine in a dose of 15 mg daily.[92] None of their enrollees, including 22 who received classic treatment, developed clinically significant leukopenia or thrombocytopenia, which contrasted with the results of their previous study.[87] Sulfadiazine

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

is a sulfonamide anti-microbial, and as such carries a risk of multiple hypersensitivity reactions, including most commonly, skin rashes.

An alternative to classic treatment, trimethoprim-sulfamethoxazole (160 mg–800 mg twice daily orally)[89] is an attractive option for reasons that include low cost, wide availability and tolerability, although sulfonamide-related reactions may occur. This drug combination has a similar mode of action to pyrimethamine and sulfadiazine on tetrahydrofolate synthesis. In 1991, Dr. Opremcak was the sole AUS member who reported trimethoprim-sulfamethoxazole as his preferred medical treatment for patients with ocular toxoplasmosis. The following year, he published a retrospective report describing positive experience treating 16 patients with ocular toxoplasmosis with trimethoprim-sulfamethoxazole alone or in combination with clindamycin or clindamycin and prednisone.[93]

The large prospective comparative trial performed by Rothova *et al.*[87] demonstrated trimethoprim-sulfamethoxazole with prednisone to be relatively well tolerated (i.e. side effects requiring discontinuation in 4% of patients), but not able to reduce lesion size to the degree of classic therapy. These treatment results contrast with those of a more recent prospective trial published by Soheilian *et al.* in 2005.[94] In that study, 59 patients with toxoplasmic retinochoroiditis were randomized to treatment with trimethoprim-sulfamethoxazole (160 mg–800 mg twice daily by mouth) and prednisolone or classic therapy. Inflammation resolved in all patients. Reduction in the size of the lesion was comparable between the two treatment groups (i.e. 59% for trimethoprim-sulfamethoxazole and 61% for classic therapy), and there was no significant difference in post-treatment visual acuity. As highlighted in an accompanying Discussion by Holland,[95] one potential concern was the use of doses of pyrimethamine and sulfadiazine that were half what is commonly given. Yet, Holland concluded that the authors had ‘provided the most convincing data to date … that trimethoprim/sulfamethoxazole/prednisone is an acceptable alternative to classic therapy’. By 2001, the number of AUS members including trimethoprim-sulfamethoxazole in their preferred treatment regimen had risen to 23%, and 10 years on, this percentage is likely higher.

Trimethoprim and sulfamethoxazole may also have a role in the prevention of recurrent attacks of ocular toxoplasmosis. Silveira *et al.*[96] found that trimethoprim-sulfamethoxazole (160 mg–800 mg), taken orally every 3 days for 20 months, significantly reduced the risk of recurrent toxoplasmic retinochoroiditis from 23.8% in untreated control subjects to 6.6%. This correspond to a ‘number needed to treat’ of 5.8 over the study period. As would be anticipated, some cutaneous toxicity occurred, and 6.6% of patients discontinued treatment for this reason. The investigators suggested a role for such preventive treatment in patients with a history of frequent and severe recurrences or with toxoplasmic scars adjacent to the fovea.

Clindamycin (300 mg orally four times daily)[89] is a lincosamide antibiotic that interferes with translation of the apicoplast, which is an unusual plastid-like organelle found in *T. gondii*.[97] The drug is often added to triple therapy, which is then referred to as ‘quadruple therapy’. In 2001, almost one third of AUS members preferred this approach to classic therapy.[89] In a retrospective study of 36 patients with active inflammation in 37 eyes, Lam

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

and Tessler[98] reported 81% of eyes responded within 3 weeks of starting quadruple therapy, as indicated by improved vision and/or markers of intraocular inflammation. In other situations, clindamycin has been substituted for pyrimethamine. For example, Tabbara and O'Connor[99] used clindamycin and sulfadiazine or clindamycin alone to manage toxoplasmic retinochoroiditis, and similarly reported 80% response within 3 weeks. On the other hand, the comparative study by Rothova *et al.*,[87] showed less reduction in lesion size in patients treated with clindamycin, sulfadiazine and corticosteroid when compared to patients who took classic therapy. Pseudomembranous colitis is a well-recognized potential complication of clindamycin, and diarrhoea required cessation of drug in an unstated number of patients in this study.

More recent studies have evaluated intravitreal injection of clindamycin and dexamethasone as local treatment for ocular toxoplasmosis.[100–103] Peyman and colleagues published the first evidence that this treatment might be effective, in the form of a case report in 1998[100] and a retrospective case series including four patients in 2001.[101] Subsequently, the description of a larger group of 12 patients treated with intravitreal clindamycin and dexamethasone alone ($n = 4$) or in combination with systemic antimicrobial agents suggested therapeutic benefit for lesions close to the macula or optic nerve.[102] In 2011, Soheilian *et al.*[103] reported the results of a well-designed prospective trial in which 68 patients with ocular toxoplasmosis involving or threatening macula or optic nerve, or adjacent to a large vessel and/or associated with severe vitritis were randomized to receive intravitreal clindamycin (1 mg) and dexamethasone (400 μg) or triple therapy. One potential limitation was dosages of pyrimethamine and sulfadiazine that were lower than are typically employed, possibly reducing effectiveness for the classic treatment arm. In the intravitreal injection group, 47% of subjects required two or three injections. If needed, injections were repeated at 2-week intervals, based on a 5.6 day half-life of intravitreal clindamycin. Mean reduction in lesion size, increase in visual acuity and decrease in vitreous inflammation were not significantly different between groups. No drug-related complications were reported for intravitreally injected eyes. Interestingly, the investigators observed significantly larger reduction in size of lesions in *T. gondii* IgM-positive patients who received classic treatment *versus* those who received intravitreal treatment. This observation was logically explained by the systemic involvement that necessarily accompanies a recently acquired infection. Local treatment appears particularly suitable for patients with recurrent infection, in whom systemic drug toxicities are a concern, such as pregnant women. On the other hand, the local approach would not be recommended in the patient who suffers from an immunodeficiency, such as AIDS.

Interest in two other anti-parasitic drugs for treatment of ocular toxoplasmosis (i.e. atovaquone [750 mg three/four times daily orally][89] and azithromycin [250 mg daily orally][89]) was stimulated by reports describing convincing activity against encysted parasites in experimental systems.[104,105] Unfortunately, however, these agents do not appear to prevent recurrent toxoplasmic retinochoroiditis in the human host, and at least in 2001, both were used infrequently in the treatment of the disease. In 1999, Pearson *et al.*,[104] conducted an single-armed, open-label, prospective trial of atovaquone in 17 immuno-competent patients with posterior pole lesions, lesions measuring over three disc diameters

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

and/or lesions associated with an endophthalmitis picture. The group reported improvement of active retinitis within 1 to 3 weeks, although visual acuity was their main outcome measure. Two patients experienced recurrent inflammation during the 10-month mean follow-up period. One patient ceased treatment for gastrointestinal side effects. A retrospective study of 41 patients treated with atovaquone for toxoplasmic retinochoroiditis documented similar tolerability, but noted reactivation in 44% of patients, with a longer follow-up interval averaging 39 months.[106] There is at least one case report of recrudescent retinochoroiditis in an immunocompetent patient which occurred 5 weeks into treatment with atovaquone, suggesting that early resistance may occur in some instances.[72]

The use of azithromycin in treatment of ocular toxoplasmosis has been addressed by two studies from Dr. Rothova's group. The first small study of 11 patients in 1998 sought to address the question of whether the drug could prevent recurrences.[105] Although 64% of treated patients experienced resolution of inflammation with demarcation of the retinal lesions within 4 weeks, 27% experienced recurrence within the first year of follow-up. On the other hand, no systemic side effects were encountered. Subsequently, these investigators evaluated the efficacy of pyrimethamine plus azithromycin *versus* classic therapy in a randomized, prospective trial of 46 patients with toxoplasmic retinitis within the temporal arcades or adjacent to the optic disc.[92] They found no difference in treatment effect between the two groups but observed significantly less frequent – and less severe – adverse events in the azithromycin-treated patients. Indeed, no patient treated with azithromycin was required to cease drug during the study for adverse events, in comparison to three patients who took classic therapy. This well-conducted study was published after the most recent survey of AUS members, and one wonders what impact it may have had on present practice patterns. The authors stated that results of this study had led them to select pyrimethamine and azithromycin as first-line treatment for sight-threatening retinochoroiditis.

In an otherwise healthy adult, the host immune response contributes substantially to the intraocular inflammation that follows tachyzoite replication within the retina. For this reason, systemic corticosteroids are routinely added to the anti-microbial cocktail in immunocompetent adults with toxoplasmic retinochoroiditis, although the doses employed and timing of administration vary widely between uveitis specialists.[89,107] Still, as highlighted by Bosch-Driessen and Rothova,[107] no study has specifically evaluated the benefit of corticosteroid as an adjunct therapy to antimicrobials or as the sole medical approach for this disease. Given without antimicrobials, as might occur in cases of initially misdiagnosed, atypical infection, systemic corticosteroid treatment has been associated with legal blindness in a majority of patients.[107] While immuno-compromised patients are generally approached similarly to immunocompetent persons with regards to antimicrobial treatment, systemic corticosteroid is usually omitted from the drug regimen in these patients.[89] They are also typically treated with some form of maintenance antimicrobial therapy, often trimethoprim-sulfamethoxazole, while the state of immunocompromise persists.

Periocular corticosteroid injections are an unpopular approach among the members of the AUS,[89] almost certainly as their administration has been associated with disastrous outcomes, particularly if administered without concomitant anti-parasitic therapy.[108] As

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

discussed above, relatively short-acting dexamethasone has been successfully combined with clindamycin as intravitreal therapy. The effective use of intravitreal use of triamcinolone acetonide, which is considerably longer acting, is reported,[109] but very poor outcome due to uncontrolled infection is also described,[110] and this approach is not standard. On the other hand, topical corticosteroid is widely prescribed for anterior uveitis in ocular toxoplasmosis.[89]

Treatment of ocular toxoplasmosis during pregnancy mandates special consideration due to the potential effects of anti-parasitic medications on the unborn child.[64] The highest risk for any medication exists during first trimester organogenesis. In a patient with recurrent ocular toxoplasmosis, the first consideration is whether treatment is actually necessary. If intervention is indicated, most ophthalmologists sensibly prefer to involve an infectious disease physician or obstetrician.[89] Local treatment with intravitreal clindamycin and dexamethasone is an obvious choice.[102,103] In their discussion of a series of four patients with ocular toxoplasmosis during pregnancy, Kump *et al.*[111] reviewed the systemic options for such patients. Classic therapy should be avoided, as pyrimethamine may be teratogenic and sulfadiazine – and other sulphonamides – may cause bilirubin encephalopathy. As alternatives, the authors suggest the combinations of clindamycin and azithromycin or clindamycin and atovaquone, with or without systemic corticosteroid.

Recurrent toxoplasmic retinochoroiditis in a pregnant woman poses minimal risk to the foetus, and treatment is not indicated for the sole purpose of preventing vertical transmission.[2] However, when infection is acquired during or immediately prior to pregnancy, there is significant risk of transmission of *T. gondii* to the foetus and congenital toxoplasmosis. The management of this difficult situation is usually coordinated by a perinatologist, and a detailed discussion of the topic is outside the scope of this review. Briefly, per Montoya and Remington,[64] if a pregnant mother becomes infected with *T. gondii* up to 18 weeks into the pregnancy or within the 6 months prior to conception, treatment with the macrolide antibiotic, spiramycin, is recommended. If maternal infection is acquired from 18 weeks into the pregnancy, when risk of transmission is high or if foetal infection is present, treatment with pyramethamine, sulfadiazine and folinic acid is advised. Continuation of treatment with these antibiotics during the first year of life, appears to reduce the occurrence of new retinal lesions.[112,113]

Conclusions

Despite many advances in the management of ocular toxoplasmosis, important clinical questions remain, especially with regard to treatment. Molecular biological advances have improved the ability to diagnose atypical presentations of the disease, and as a result, numerous patients have undoubtedly benefited from earlier intervention, particularly in the context of immunosuppression. On the other hand, as is well stated by Holland,[95] ‘the fundamental overriding question’ that still lacks an answer is: ‘does any therapy alter the natural history of toxoplasmic retinochoroiditis in patients with normal immune function?’ If treatment benefit exists, the differential effectiveness of various agents is not clearly defined. Moreover, the search for a safe drug with effective cysticidal activity in humans, which theoretically would eliminate disease recurrences, has not been fruitful to date.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Additional prospective clinical trials, which randomize patients to various treatment strategies, including no intervention, are indicated. At the same time, clinicians continue to rely on basic scientists to identify more effective therapeutic agents with minimal potential for toxicity. Today, ocular toxoplasmosis remains one of the most significant intraocular infections for the human population.

Acknowledgments

Funding sources: Supported in part by NEI/NIH (R21 EY019550), Research to Prevent Blindness (unrestricted grant to Casey Eye Institute), and the Schnitzer Novack Foundation.

References

1. Wilder HC. Toxoplasma chorioretinitis in adults. AMA Arch Ophthalmol. 1952; 48:127–36. [PubMed: 14943320]
2. Holland, GN.; O'Connor, GR.; Belfort, R., Junior; Remington, JS. Toxoplasmosis. In: Pepose, JS.; Holland, GN.; Wilhelmus, KR., editors. Ocular Infection & Immunity. St. Louis: Mosby; 1996. p. 1183-223.
3. Holland GN. Ocular toxoplasmosis: a global reassessment. Part II: disease manifestations and management. Am J Ophthalmol. 2004; 137:1–17. [PubMed: 14700638]
4. Friedmann CT, Knox DL. Variations in recurrent active toxoplasmic retinochoroiditis. Arch Ophthalmol. 1969; 81:481–93. [PubMed: 5777756]
5. Bosch-Driessen LE, Berendschot TT, Ongkosuwito JV, Rothova A. Ocular toxoplasmosis: clinical features and prognosis of 154 patients. Ophthalmology. 2002; 109:869–78. [PubMed: 11986090]
6. Johnson MW, Greven GM, Jaffe GJ, Sudhalkar H, Vine AK. Atypical, severe toxoplasmic retinochoroiditis in elderly patients. Ophthalmology. 1997; 104:48–57. [PubMed: 9022104]
7. Montoya JG, Remington JS. Toxoplasmic chorioretinitis in the setting of acute acquired toxoplasmosis. Clin Infect Dis. 1996; 23:277–82. [PubMed: 8842263]
8. Bonfioli AA, Orefice F. Toxoplasmosis. Semin Ophthalmol. 2005; 20:129–41. [PubMed: 16282146]
9. Dodds EM, Holland GN, Stanford MR, et al. Intraocular inflammation associated with ocular toxoplasmosis: relationships at initial examination. Am J Ophthalmol. 2008; 146:856–65. e2. [PubMed: 19027421]
10. Theodossiadis P, Kokolakis S, Ladas I, Kollia AC, Chatzoulis D, Theodossiadis G. Retinal vascular involvement in acute toxoplasmic retinochoroiditis. Int Ophthalmol. 1995; 19:19–24. [PubMed: 8537191]
11. Smith JR, Cunningham ET Jr. Atypical presentations of ocular toxoplasmosis. Curr Opin Ophthalmol. 2002; 13:387–92. [PubMed: 12441842]
12. Westfall AC, Lauer AK, Suhler EB, Rosenbaum JT. Toxoplasmosis retinochoroiditis and elevated intraocular pressure: a retrospective study. J Glaucoma. 2005; 14:3–10. [PubMed: 15650597]
13. Borruat FX, Kapoor R, Sanders MD. Simultaneous retinal and optic nerve lesions in toxoplasmosis: the advantages of magnetic resonance imaging. Br J Ophthalmol. 1993; 77:450–2. [PubMed: 8343477]
14. Song A, Scott IU, Davis JL, Lam BL. Atypical anterior optic neuropathy caused by toxoplasmosis. Am J Ophthalmol. 2002; 133:162–4. [PubMed: 11755864]
15. Eckert GU, Melamed J, Menegaz B. Optic nerve changes in ocular toxoplasmosis. Eye (Lond). 2007; 21:746–51. [PubMed: 16575416]
16. Roach ES, Zimmerman CF, Troost BT, Weaver RG. Optic neuritis due to acquired toxoplasmosis. Pediatr Neurol. 1985; 1:114–6. [PubMed: 3880394]
17. Grossniklaus HE, Specht CS, Allaire G, Leavitt JA. Toxoplasma gondii retinochoroiditis and optic neuritis in acquired immune deficiency syndrome. Report of a case. Ophthalmology. 1990; 97:1342–6. [PubMed: 2243685]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

18. Doft BH, Gass DM. Punctate outer retinal toxoplasmosis. Arch Ophthalmol. 1985; 103:1332–6. [PubMed: 4038125]
19. Doft BH, Gass JD. Outer retinal layer toxoplasmosis. Graefes Arch Clin Exp Ophthalmol. 1986; 224:78–82. [PubMed: 3943742]
20. Matthews JD, Weiter JJ. Outer retinal toxoplasmosis. Ophthalmology. 1988; 95:941–6. [PubMed: 3174045]
21. Moraes HV Jr. Punctate outer retinal toxoplasmosis in an HIV-positive child. Ocul Immunol Inflamm. 1999; 7:93–5. [PubMed: 10420204]
22. Moreno RJ, Weisman J, Waller S. Neuroretinitis: an unusual presentation of ocular toxoplasmosis. Ann Ophthalmol. 1992; 24:68–70. [PubMed: 1562128]
23. Fish RH, Hoskins JC, Kline LB. Toxoplasmosis neuroretinitis. Ophthalmology. 1993; 100:1177–82. [PubMed: 8341498]
24. Frezzotti R, Berengo A, Guerra R, Cavalllini F. Toxoplasmic coats' retinitis. a parasitologically proved case. Am J Ophthalmol. 1965; 59:1099–102. [PubMed: 14292723]
25. Silveira C, Belfort R Jr, Nussenblatt R, et al. Unilateral pigmentary retinopathy associated with ocular toxoplasmosis. Am J Ophthalmol. 1989; 107:682–4. [PubMed: 2729419]
26. Morgan CM, Gragoudas ES. Branch retinal artery occlusion associated with recurrent toxoplasmic retinochoroiditis. Arch Ophthalmol. 1987; 105:130–1. [PubMed: 3800730]
27. Tandon R, Menon V, Das GK, Verma L. Toxoplasmic papillitis with central retinal artery occlusion. Can J Ophthalmol. 1995; 30:374–6. [PubMed: 8963940]
28. Hayashi S, Kim MK, Belfort R Jr. White-centered retinal hemorrhages in ocular toxoplasmosis. Retina. 1997; 17:351–2. [PubMed: 9279954]
29. Kraushar MF, Gluck SB, Pass S. Toxoplasmic retinochoroiditis presenting as serous detachment of the macula. Ann Ophthalmol. 1979; 11:1513–4. [PubMed: 555845]
30. Schuman JS, Weinberg RS, Ferry AP, Guerry RK. Toxoplasmic scleritis. Ophthalmology. 1988; 95:1399–403. [PubMed: 3226688]
31. Holland GN, Muccioli C, Silveira C, Weisz JM, Belfort R Jr, O'Connor GR. Intraocular inflammatory reactions without focal necrotizing retinochoroiditis in patients with acquired systemic toxoplasmosis. Am J Ophthalmol. 1999; 128:413–20. [PubMed: 10577581]
32. Rehder JR, Burnier MB Jr, Pavesio CE, et al. Acute unilateral toxoplasmic iridocyclitis in an AIDS patient. Am J Ophthalmol. 1988; 106:740–1. [PubMed: 3195654]
33. Toledo de Abreu M, Belfort R Jr, Hirata PS. Fuchs' heterochromic cyclitis and ocular toxoplasmosis. Am J Ophthalmol. 1982; 93:739–44. [PubMed: 7201246]
34. Schwab IR. The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis. Am J Ophthalmol. 1991; 111:356–62. [PubMed: 2000906]
35. Arffa RC, Schlaegel TF Jr. Chorioretinal scars in Fuchs' heterochromic iridocyclitis. Arch Ophthalmol. 1984; 102:1153–5. [PubMed: 6331819]
36. La Hey E, Rothova A, Baarsma GS, de Vries J, van Knapen F, Kijlstra A. Fuchs' heterochromic iridocyclitis is not associated with ocular toxoplasmosis. Arch Ophthalmol. 1992; 110:806–11. [PubMed: 1596229]
37. Hovakimyan A, Cunningham ET Jr. Ocular toxoplasmosis. Ophthalmol Clin North Am. 2002; 15:327–32. [PubMed: 12434481]
38. Lassoued S, Zabraniecki L, Marin F, Billey T. Toxoplasmic chorioretinitis and antitumor necrosis factor treatment in rheumatoid arthritis. Semin Arthritis Rheum. 2007; 36:262–3. [PubMed: 17067660]
39. Nicholson DH, Wolchok EB. Ocular toxoplasmosis in an adult receiving long-term corticosteroid therapy. Arch Ophthalmol. 1976; 94:248–54. [PubMed: 1252177]
40. Yeo JH, Jakobiec FA, Iwamoto T, Richard G, Kreissig I. Opportunistic toxoplasmic retinochoroiditis following chemotherapy for systemic lymphoma. A light and electron microscopic study. Ophthalmology. 1983; 90:885–98. [PubMed: 6634071]
41. Singer MA, Hagler WS, Grossniklaus HE. Toxoplasma gondii retinochoroiditis after liver transplantation. Retina. 1993; 13:40–5. [PubMed: 8460279]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

42. Cochereau-Massin I, LeHoang P, Lautier-Frau M, et al. Ocular toxoplasmosis in human immunodeficiency virus-infected patients. Am J Ophthalmol. 1992; 114:130–5. [PubMed: 1322640]
43. Holland GN, Engstrom RE Jr, Glasgow BJ, et al. Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol. 1988; 106:653–67. [PubMed: 3195645]
44. Moorthy RS, Smith RE, Rao NA. Progressive ocular toxoplasmosis in patients with acquired immunodeficiency syndrome. Am J Ophthalmol. 1993; 115:742–7. [PubMed: 8506909]
45. Rodgers CA, Harris JR. Ocular toxoplasmosis in HIV infection. Int J STD AIDS. 1996; 7:307–9. [PubMed: 8894817]
46. Labalette P, Delhaes L, Margaron F, Fortier B, Rouland JF. Ocular toxoplasmosis after the fifth decade. Am J Ophthalmol. 2002; 133:506–15. [PubMed: 11931784]
47. Cunningham ET Jr, Margolis TP. Ocular manifestations of HIV infection. N Engl J Med. 1998; 339:236–44. [PubMed: 9673303]
48. Balansard B, Bodaghi B, Cassoux N, et al. Necrotising retinopathies simulating acute retinal necrosis syndrome. Br J Ophthalmol. 2005; 89:96–101. [PubMed: 15615755]
49. Moshfeghi DM, Dodds EM, Couto CA, et al. Diagnostic approaches to severe, atypical toxoplasmosis mimicking acute retinal necrosis. Ophthalmology. 2004; 111:716–25. [PubMed: 15051204]
50. Elkins BS, Holland GN, Opremcak EM, et al. Ocular toxoplasmosis misdiagnosed as cytomegalovirus retinopathy in immunocompromised patients. Ophthalmology. 1994; 101:499–507. [PubMed: 8127570]
51. Mets MB, Holfels E, Boyer KM, et al. Eye manifestations of congenital toxoplasmosis. Am J Ophthalmol. 1996; 122:309–24. [PubMed: 8794703]
52. Delair E, Monnet D, Grabar S, Dupouy-Camet J, Yera H, Brézin AP. Respective roles of acquired and congenital infections in presumed ocular toxoplasmosis. Am J Ophthalmol. 2008; 146:851–5. [PubMed: 18723143]
53. Bosch-Driessen LH, Karimi S, Stilma JS, Rothova A. Retinal detachment in ocular toxoplasmosis. Ophthalmology. 2000; 107:36–40. [PubMed: 10647716]
54. Bosch-Driessen LH, Plaisier MB, Stilma JS, Van der Lelij A, Rothova A. Reactivations of ocular toxoplasmosis after cataract extraction. Ophthalmology. 2002; 109:41–5. [PubMed: 11772577]
55. Gentile RC, Berinstein DM, Oppenheim R, Walsh JB. Retinal vascular occlusions complicating acute toxoplasmic retinochoroiditis. Can J Ophthalmol. 1997; 32:354–8. [PubMed: 9276124]
56. Holland GN, Crespi CM, ten Dam-van Loon N, et al. Analysis of recurrence patterns associated with toxoplasmic retinochoroiditis. Am J Ophthalmol. 2008; 145:1007–13. [PubMed: 18343351]
57. Garweg JG, Scherrer JN, Halberstadt M. Recurrence characteristics in European patients with ocular toxoplasmosis. Br J Ophthalmol. 2008; 92:1253–6. [PubMed: 18211930]
58. Pivetti-Pezzi P, Accorinti M, Tamburi S, Ciapparoni V, Abdulaziz MA. Clinical features of toxoplasmic retinochoroiditis in patients with acquired immunodeficiency syndrome. Ann Ophthalmol. 1994; 26:73–84. [PubMed: 7944160]
59. Morhun PJ, Weisz JM, Elias SJ, Holland GN. Recurrent ocular toxoplasmosis in patients treated with systemic corticosteroids. Retina. 1996; 16:383–7. [PubMed: 8912963]
60. Hodge WG, Seiff SR, Margolis TP. Ocular opportunistic infection incidences among patients who are HIV positive compared to patients who are HIV negative. Ophthalmology. 1998; 105:895–900. [PubMed: 9593394]
61. Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. Lancet. 1999; 353:1829–33. [PubMed: 10359407]
62. Montoya JG, Liesenfeld O. Toxoplasmosis. Lancet. 2004; 363:1965–76. [PubMed: 15194258]
63. Silveira C, Ferreira R, Muccioli C, Nussenblatt R, Belfort R Jr. Toxoplasmosis transmitted to a newborn from the mother infected 20 years earlier. Am J Ophthalmol. 2003; 136:370–1. [PubMed: 12888070]
64. Montoya JG, Remington JS. Management of Toxoplasma gondii infection during pregnancy. Clin Infect Dis. 2008; 47:554–66. [PubMed: 18624630]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

65. Akstein RB, Wilson LA, Teutsch SM. Acquired toxoplasmosis. Ophthalmology. 1982; 89:1299–302. [PubMed: 7162776]
66. Oksenhendler E, Charreau I, Tournerie C, Azihary M, Carbon C, Aboulker JP. Toxoplasma gondii infection in advanced HIV infection. AIDS. 1994; 8:483–7. [PubMed: 8011251]
67. Hogan, MJ. Ocular Toxoplasmosis. New York: Columbia University Press; 1951.
68. Roberts F, Mets MB, Ferguson DJ, et al. Histopathological features of ocular toxoplasmosis in the fetus and infant. Arch Ophthalmol. 2001; 119:51–8. [PubMed: 11146726]
69. Brézin AP, Kasner L, Thulliez P, et al. Ocular toxoplasmosis in the fetus. Immunohistochemistry analysis and DNA amplification Retina. 1994; 14:19–26.
70. Parke DW 2nd, Font RL. Diffuse toxoplasmic retinochoroiditis in a patient with AIDS. Arch Ophthalmol. 1986; 104:571–5. [PubMed: 3954664]
71. Rao NA, Font RL. Toxoplasmic retinochoroiditis: electron-microscopic and immunofluorescence studies of formalin-fixed tissue. Arch Ophthalmol. 1977; 95:273–7. [PubMed: 319779]
72. Baatz H, Mirshahi A, Puchta J, Gumbel H, Hattenbach LO. Reactivation of toxoplasma retinochoroiditis under atovaquone therapy in an immunocompetent patient. Ocul Immunol Inflamm. 2006; 14:185–7. [PubMed: 16766403]
73. Zimmerman LE. Ocular pathology of toxoplasmosis. Surv Ophthalmology. 1961; 6:832–56.
74. Harper TW, Miller D, Schiffman JC, Davis JL. Polymerase chain reaction analysis of aqueous and vitreous specimens in the diagnosis of posterior segment infectious uveitis. Am J Ophthalmol. 2009; 147:140–7. e2. [PubMed: 18834576]
75. Rothova A, de Boer JH, Ten Dam-van Loon NH, et al. Usefulness of aqueous humor analysis for the diagnosis of posterior uveitis. Ophthalmology. 2008; 115:306–11. [PubMed: 17669497]
76. Van Gelder RN. CME review: polymerase chain reaction diagnostics for posterior segment disease. Retina. 2003; 23:445–52. [PubMed: 12972753]
77. Cassaing S, Bessieres MH, Berry A, Berrebi A, Fabre R, Magnaval JF. Comparison between two amplification sets for molecular diagnosis of toxoplasmosis by real-time PCR. J Clin Microbiol. 2006; 44:720–4. [PubMed: 16517845]
78. Chan CC, Palestine AG, Li Q, Nussenblatt RB. Diagnosis of ocular toxoplasmosis by the use of immuno-cytology and the polymerase chain reaction. Am J Ophthalmol. 1994; 117:803–5. [PubMed: 7911007]
79. Montoya JG, Parmley S, Liesenfeld O, Jaffe GJ, Remington JS. Use of the polymerase chain reaction for diagnosis of ocular toxoplasmosis. Ophthalmology. 1999; 106:1554–63. [PubMed: 10442904]
80. Westeneng AC, Rothova A, de Boer JH, de Groot-Mijnes JD. Infectious uveitis in immunocompromised patients and the diagnostic value of polymerase chain reaction and Goldmann-Witmer coefficient in aqueous analysis. Am J Ophthalmol. 2007; 144:781–5. [PubMed: 17707328]
81. De Groot-Mijnes JD, Rothova A, Van Loon AM, et al. Polymerase chain reaction and Goldmann-Witmer coefficient analysis are complimentary for the diagnosis of infectious uveitis. Am J Ophthalmol. 2006; 141:313–8. [PubMed: 16458686]
82. de Boer JH, Luyendijk L, Rothova A, Kijlstra A. Analysis of ocular fluids for local antibody production in uveitis. Br J Ophthalmol. 1995; 79:610–6. [PubMed: 7626580]
83. Fardeau C, Romand S, Rao NA, et al. Diagnosis of toxoplasmic retinochoroiditis with atypical clinical features. Am J Ophthalmol. 2002; 134:196–203. [PubMed: 12140026]
84. Fekkar A, Bodaghi B, Touafek F, Le Hoang P, Mazier D, Paris L. Comparison of immunoblotting, calculation of the Goldmann-Witmer coefficient, and realtime PCR using aqueous humor samples for diagnosis of ocular toxoplasmosis. J Clin Microbiol. 2008; 46:1965–7. [PubMed: 18400917]
85. Villard O, Filisetti D, Roch-Deries F, Garweg J, Flament J, Candolfi E. Comparison of enzyme-linked immunosorbent assay, immunoblotting, and PCR for diagnosis of toxoplasmic chorioretinitis. J Clin Microbiol. 2003; 41:3537–41. [PubMed: 12904352]
86. Ronday MJ, Luyendijk L, Baarsma GS, Bollemeijer JG, Van der Lelij A, Rothova A. Presumed acquired ocular toxoplasmosis. Arch Ophthalmol. 1995; 113:1524–9. [PubMed: 7487620]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

87. Rothova A, Meenken C, Buitenhuis HJ, et al. Therapy for ocular toxoplasmosis. Am J Ophthalmol. 1993; 115:517–23. [PubMed: 8470726]
88. Stanford MR, See SE, Jones LV, Gilbert RE. Antibiotics for toxoplasmic retinochoroiditis: an evidence-based systematic review. Ophthalmology. 2003; 110:926–31. quiz 31–2. [PubMed: 12750091]
89. Holland GN, Lewis KG. An update on current practices in the management of ocular toxoplasmosis. Am J Ophthalmol. 2002; 134:102–14. [PubMed: 12095816]
90. Engstrom RE Jr, Holland GN, Nussenblatt RB, Jabs DA. Current practices in the management of ocular toxoplasmosis. Am J Ophthalmol. 1991; 111:601–10. [PubMed: 2021170]
91. Hogan MJ. Ocular toxoplasmosis. Trans Am Acad Ophthalmol Otolaryngol. 1958; 62:7–37. [PubMed: 13529989]
92. Bosch-Driessen LH, Verbraak FD, Suttorp-Schulten MS, et al. A prospective, randomized trial of pyrimethamine and azithromycin vs pyrimethamine and sulfadiazine for the treatment of ocular toxoplasmosis. Am J Ophthalmol. 2002; 134:34–40. [PubMed: 12095805]
93. Opremcak EM, Scales DK, Sharpe MR. Trimethoprim-sulfamethoxazole therapy for ocular toxoplasmosis. Ophthalmology. 1992; 99:920–5. [PubMed: 1630782]
94. Soheilian M, Sadoughi MM, Ghajarnia M, et al. Prospective randomized trial of trimethoprim/sulfamethoxazole versus pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis. Ophthalmology. 2005; 112:1876–82. [PubMed: 16171866]
95. Holland GN. Prospective, randomized trial of trimethoprim/sulfamethoxazole vs. pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis: discussion. Ophthalmology. 2005; 112:1882–4. [PubMed: 16271316]
96. Silveira C, Belfort R Jr, Muccioli C, et al. The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis. Am J Ophthalmol. 2002; 134:41–6. [PubMed: 12095806]
97. Camps M, Arrizabalaga G, Boothroyd J. An rRNA mutation identifies the apicoplast as the target for clindamycin in Toxoplasma gondii. Mol Microbiol. 2002; 43:1309–18. [PubMed: 11918815]
98. Lam S, Tessler HH. Quadruple therapy for ocular toxoplasmosis. Can J Ophthalmol. 1993; 28:58–61. [PubMed: 8508337]
99. Tabbara KF, O'Connor GR. Treatment of ocular toxoplasmosis with clindamycin and sulfadiazine. Ophthalmology. 1980; 87:129–34. [PubMed: 7383542]
100. Martinez CE, Zhang D, Conway MD, Peyman GA. Successful management of ocular toxoplasmosis during pregnancy using combined intraocular clindamycin and dexamethasone with systemic sulfadiazine. Int Ophthalmol. 1998; 22:85–8. [PubMed: 10472767]
101. Kishore K, Conway MD, Peyman GA. Intravitreal clindamycin and dexamethasone for toxoplasmic retinochoroiditis. Ophthalmic Surg Lasers. 2001; 32:183–92. [PubMed: 11371084]
102. Lasave AF, Diaz-Llopis M, Muccioli C, Belfort R Jr, Arevalo JF. Intravitreal clindamycin and dexamethasone for zone 1 toxoplasmic retinochoroiditis at twenty-four months. Ophthalmology. 2010; 117:1831–8. [PubMed: 20471684]
103. Soheilian M, Ramezani A, Azimzadeh A, et al. Randomized trial of intravitreal clindamycin and dexamethasone versus pyrimethamine, sulfadiazine, and prednisolone in treatment of ocular toxoplasmosis. Ophthalmology. 2011; 118:134–41. [PubMed: 20708269]
104. Pearson PA, Piracha AR, Sen HA, Jaffe GJ. Atova-quone for the treatment of toxoplasma retinochoroiditis in immunocompetent patients. Ophthalmology. 1999; 106:148–53. [PubMed: 9917796]
105. Rothova A, Bosch-Driessen LE, van Loon NH, Treffers WF. Azithromycin for ocular toxoplasmosis. Br J Ophthalmol. 1998; 82:1306–8. [PubMed: 9924338]
106. Winterhalter S, Severing K, Stammen J, Maier AK, Godehardt E, Joussen AM. Does atovaquone prolong the disease-free interval of toxoplasmic retinochoroiditis? Graefes Arch Clin Exp Ophthalmol. 2010; 248:1187–92. [PubMed: 20437247]
107. Bosch-Driessen EH, Rothova A. Sense and nonsense of corticosteroid administration in the treatment of ocular toxoplasmosis. Br J Ophthalmol. 1998; 82:858–60. [PubMed: 9828766]
108. Nozik RA. Results of treatment of ocular toxoplasmosis with injectable corticosteroids. Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol. 1977; 83:811–8.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

109. Aggio FB, Muccioli C, Belfort R Jr. Intravitreal triamcinolone acetonide as an adjunct in the treatment of severe ocular toxoplasmosis. Eye (Lond). 2006; 20:1080–2. [PubMed: 16200054]

110. Backhouse O, Bhan KJ, Bishop F. Intravitreal triamcinolone acetonide as an adjunct in the treatment of severe ocular toxoplasmosis. Eye (Lond). 2008; 22:1201–2. author reply 0-1. [PubMed: 18259204]

111. Kump LI, Androudi SN, Foster CS. Ocular toxoplasmosis in pregnancy. Clin Experiment Ophthalmol. 2005; 33:455–60. [PubMed: 16181268]

112. Phan L, Kasza K, Jalbrzikowski J, et al. Longitudinal study of new eye lesions in children with toxoplasmosis who were not treated during the first year of life. Am J Ophthalmol. 2008; 146:375–84. [PubMed: 18619570]

113. Phan L, Kasza K, Jalbrzikowski J, et al. Longitudinal study of new eye lesions in treated congenital toxoplasmosis. Ophthalmology. 2008; 115:553–9. e8. [PubMed: 17825418]