Chapter 6
Intraocular Infection

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Introduction

Intraocular infections are uncommon but potentially devastating to vision and to the eye. There is a broad range of pathogens that can cause infection in the eye. Intraocular infections can be grouped into two categories: *exogenous*, those caused by introduction of pathogens through penetration of the eye wall, or *endogenous*, those caused by introduction of the pathogen through the bloodstream to the eye [1]. Exogenous infections can be introduced via surgery, intraocular injection of medication, or trauma, and pathogens are typically either bacterial or fungal in nature [2–6]. Endogenous infections are caused by introduction of a systemic infection to the eye via the ophthalmic (usually choroidal) circulation, and therefore pathogens can be much more varied and include bacteria, fungi, viruses, protozoa, and other parasites. This chapter categorizes and describes different types of intraocular infections and their treatments.

Exogenous Endophthalmitis

Exogenous endophthalmitis is one of the most dreaded complications of intraocular surgery, intravitreal injection, or penetrating ocular trauma. It is most often classified based on the mechanism of introduction, as different organisms are associated with different mechanisms of introduction into the eye. Postoperative endophthalmitis usually presents after recent intraocular surgery, but it can also have a delayed presentation or can be associated with distant surgery (e.g., bleb-associated

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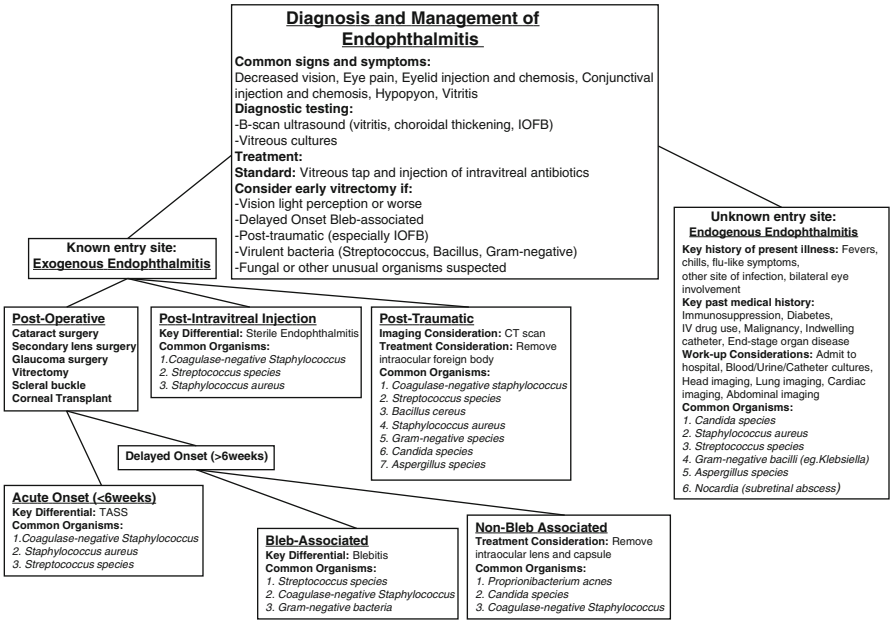

Fig. 6.1 Diagnosis and management of endophthalmitis. *IOFB* intraocular foreign body, *TASS* toxic anterior segment syndrome

endophthalmitis). Post-injection endophthalmitis has become more common with the advent of intravitreal injections for treatment of a variety of ocular diseases. Posttraumatic endophthalmitis is rare but can be associated with a greater variety of bacteria as well as fungi. Distinguishing features of these various types of exogenous endophthalmitis are discussed in more detail below, but many of the presenting features and management decisions are similar. For a summary of diagnosis and management of endophthalmitis, see Fig. 6.1.

Presentation

Patients with exogenous endophthalmitis most commonly present with blurred vision after a known introductory event, whether it be surgery, intraocular injection, or trauma [1–7]. Other symptoms include ocular pain, conjunctival or eyelid redness and/or swelling, ocular irritation, and/or photophobia. Onset may be acute (<6 weeks) or delayed (>6 weeks) after the inciting event [8]. Signs of infection on ophthalmic examination may include decreased visual acuity, relative afferent papillary defect, increased or decreased intraocular pressure, conjunctival and/or eyelid injection and chemosis, anterior chamber inflammation, hypopyon, vitritis on examination and B-scan ultrasound, and choroidal thickening (Figs. 6.2, 6.3, and 6.4). If the retina is visible in the eyes with endophthalmitis, retinal hemorrhages, nerve fiber layer infarcts, retinitis, perivasculitis, and subretinal exudation may also be seen [9]. More virulent organisms are associated with a more guarded prognosis [10] and should be suspected if there is an early presentation (<3 days after inciting

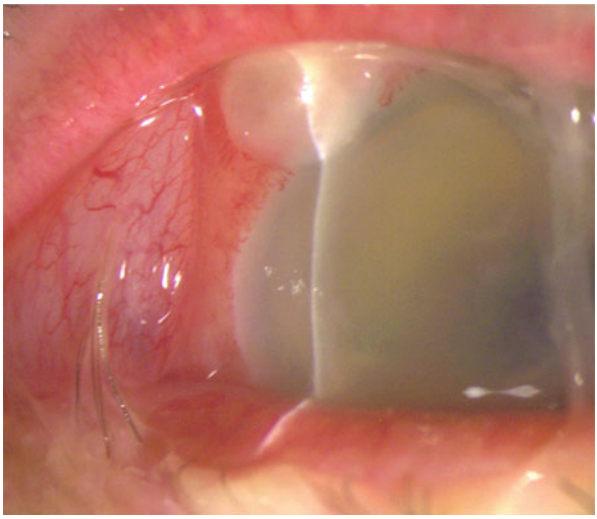

Fig. 6.2 Bleb-associated endophthalmitis. Cultures grew out *Streptococcus pneumoniae*. Purulent material is visible within the bleb. There is severe ecchymosis and chemosis of the conjunctiva. The cornea is edematous, and there is a severe anterior chamber reaction

event), trauma as the inciting event, severe eye pain, very poor visual acuity on presentation (light perception or no light perception), low intraocular pressure, conjunctival and/or eyelid chemosis, and/or dense intraocular inflammation.

Diagnostic Testing

B-scan ultrasound is often useful to detect presence and amount of vitritis. Choroidal thickening on B-scan is a poor prognostic sign. Intraocular foreign bodies may be visualized using B-scan, although radiographic imaging is often warranted in posttraumatic cases suspected of having intraocular foreign material.

A vitreous or aqueous tap is often performed at the time of intravitreal antibiotic injection. This procedure is not only helpful in allowing more space for intravitreal fluid to be injected, but the specimen may also be sent for stain and culture [1, 3, 7, 11]. Vitreous cultures may have higher yield after pars plana vitrectomy (PPV) cases with difficult-to-culture organisms, such as in fungal endophthalmitis; however, the Endophthalmitis Vitrectomy Study (EVS) showed no difference in culture positivity between the tap and PPV groups [12].

In acute postoperative endophthalmitis, vitreous cultures may be negative in up to 30 % of cases [1, 13]; aqueous cultures are more often negative than vitreous cultures. In fact, in one study, 50 % of eyes that had negative aqueous cultures had positive vitreous cultures [14]. Vitreous cultures in delayed-onset postoperative endophthalmitis are often negative. In post-injection endophthalmitis, the percentage of negative vitreous cultures is higher than in postoperative endophthalmitis (50 % vs. 75 % culture-positive rates) [15]. This may be due to an increased percentage of sterile or noninfectious endophthalmitis cases included in these numbers.

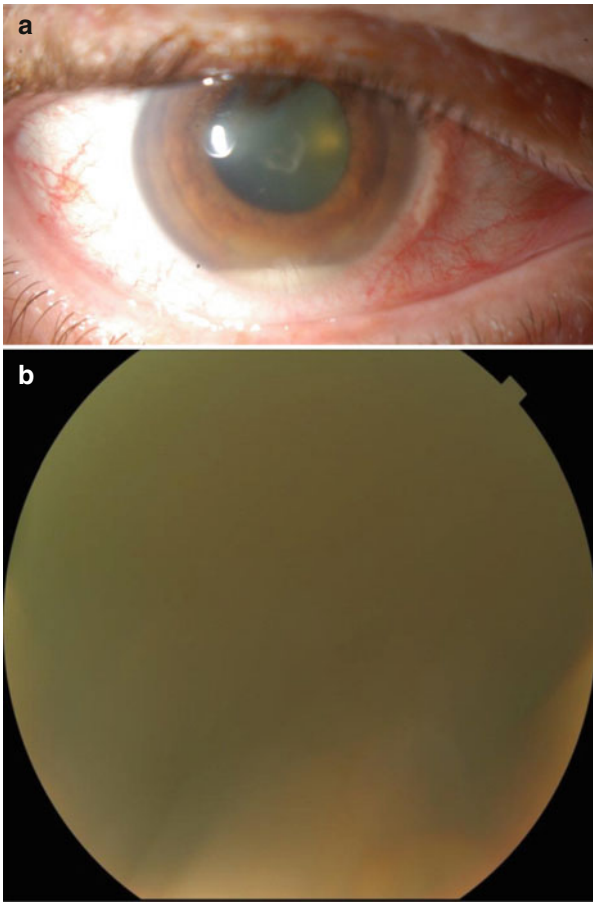

Fig. 6.3 Endogenous bacterial endophthalmitis. (**a**) There is mild corneal edema, moderate anterior chamber fibrin and white cells, and a 3 mm hypopyon. (**b**) Dense vitritis is evident (Fig. 6.2b). Cultures of the vitreous were negative, but a wrist abscess was present and grew methicillin-resistant *Staphylococcus aureus* (MRSA). The patient also had uncontrolled diabetes mellitus

Treatment

Because it is rare, much of our understanding of the treatment of endophthalmitis has come from retrospective case series. One of the largest and well-known prospective studies of endophthalmitis was the Endophthalmitis Vitrectomy Study (EVS), which was a large multicenter prospective interventional randomized controlled trial funded by the National Institute of Health, which compared intravitreal antibiotic injection alone to pars plana vitrectomy with intravitreal antibiotic injection for treatment of lens surgery-related postoperative endophthalmitis [7]. Although the study was only specific to acute post-cataract surgery endophthalmitis, many discoveries by the EVS have been used to generally guide treatment for

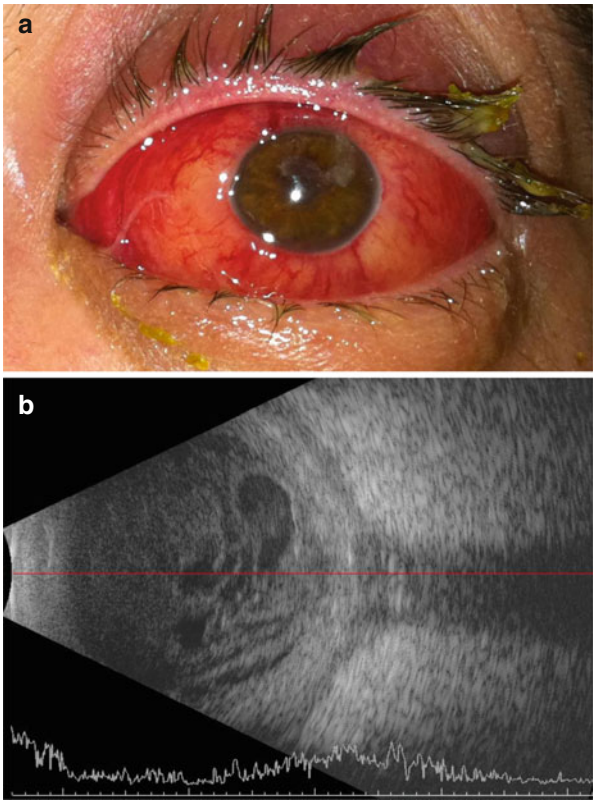

Fig. 6.4 Endogenous bacterial endophthalmitis. Infection was due to *Escherichia coli* from a liver abscess. (**a**) There is severe eyelid and conjunctival erythema and chemosis, dense microcystic corneal edema, neovascularization of the iris, severe anterior chamber inflammation, and no view to the posterior pole. (**b**) A B-scan ultrasound showed dense vitritis and severe choroidal and scleral thickening with a "T-sign" (Fig. 6.3b)

endophthalmitis. In general, the clearest evidence for prophylaxis to prevent endophthalmitis has been with the use of povidone iodine [16, 17].

Patients with suspected endophthalmitis should be treated acutely with intravitreal injections of antibacterial antibiotics with broad gram-positive and gram-negative coverage [1, 3, 7, 11]. Most studies have recommended use of vancomycin (1 mg/0.1 ml) in addition to a broad-spectrum cephalosporin, usually ceftazidime (2.25 mg/0.1 ml). This combination of medications has been shown to cover nearly 100 % of organisms in culture-positive bacterial endophthalmitis [18, 19]. If the patient is allergic to penicillins, amikacin (0.4 mg/0.1 ml), which also has excellent gram-negative coverage, may be substituted for ceftazidime. Addition of intravitreal clindamycin (450 ug/0.1 ml) may be considered for penicillin-resistant strains of

Table 6.1 Doses of common intravitreal antibiotics

Antibacterial	
Vancomycin	1 mg/0.1 ml
Ceftazidime	2.25 mg/0.1 ml
Amikacin	400 μg/0.1 ml
Clindamycin	450 μg/0.1 ml
Antifungal	
Amphotericin B	5–10 μg/0.1 ml
Voriconazole	50–100 μg/0.1 ml
Antiviral	
Foscarnet	2.4 mg/0.1 ml
Ganciclovir	2 mg/0.1 ml

bacteria [11]. Antibiotic doses are summarized in Table 6.1. If the post-injection or postoperative course does not improve after 2–3 days, a repeat intravitreal injection may be given, and the possibility of a resistant or fungal infection, or a masquerade syndrome, should also be considered.

A short course of systemic antibiotics may also be considered in the case of a particularly severe infection or associated with trauma, either a third- or fourth-generation oral fluoroquinolone, such as moxifloxacin, which have excellent intraocular penetration, or intravenous antibiotics with broad coverage for suspected organisms [11, 20, 21]. It is unclear if systemic antibiotics play an additional role in routine treatment for exogenous endophthalmitis. Notably, the EVS showed that intravenous antibiotics did not provide significant visual benefits, and the cost and risk of hospital stay outweighed the small theoretical benefit of intravenous antibiotics in most cases [7].

Topical antibiotics are typically used during the initial treatment period. Either fortified antibiotics such as vancomycin and ceftazidime or tobramycin may be used or fourth-generation fluoroquinolones such as moxifloxacin or gatifloxacin may be used. Topical administration of antibiotics should be frequent in cases of post-traumatic, bleb-associated, or postoperative endophthalmitis, particularly in cases where there appears to be active infection at the wound or entry site into the eye [11, 22].

Fungal endophthalmitis is treated similarly to bacterial endophthalmitis, with antibiotics that target the most common species of intraocular infection (*Candida*, *Aspergillus*, and *Fusarium*, followed by other species) [23, 24]. Intravitreal amphotericin B (5–10 μg/0.1 ml) combined with systemic antifungal medication is often used to treat exogenous fungal endophthalmitis [11, 23]. Intravenous antifungal medication, such as amphotericin B, may be considered, although oral antifungal medications such as fluconazole or voriconazole also have good intraocular penetration and have lower toxicity profiles. Instead of intravitreal amphotericin B, which has been shown to have retinal toxicity at higher concentrations, intravitreal voriconazole (50–100 ug/0.1 ml) may be used to successfully treat fungal endophthalmitis; voriconazole may be particularly helpful in cases of drug-resistant fungal infections [24, 25].

If the patient is suspected to have a particularly virulent organism, or if the vision is extremely poor on presentation (light perception or no light perception), urgent pars plana vitrectomy (PPV) with anterior chamber and vitreous washout and intravitreal antibiotic injection should be considered. The role of vitrectomy in endophthalmitis is similar to the role of incision and drainage of infection in other regions of the body. Vitrectomy can decrease the pathogen load and remove toxins and inflammatory material from the eye, remove the vitreous scaffolding, and may help clear the media more quickly [7, 26, 27].

Notably, the EVS showed that visual outcomes were better in acute postoperative endophthalmitis patients with LP or NLP vision treated with PPV with intravitreal antibiotics versus intravitreal antibiotic injection alone; this benefit was not seen in the eyes with better than LP vision [7]. PPV is likely helpful in cases of infection with particularly toxigenic or pathogenic organisms, such as *Streptococcus* species or gram-negative bacteria [27]. However, PPV performed during the acute infectious phase is often limited due to difficulty with visualization and can be associated with higher risk of retinal detachment during the postoperative period than vitrectomy for other conditions [11].

Intravitreal steroids (dexamethasone 0.4 mg/0.1 cc) have been used by some physicians to treat acute endophthalmitis. The rationale has been to decrease the amount of inflammatory damage to the retina; however, the utility of intravitreal steroids in the setting of endophthalmitis has been debated [28, 29]. If there is a possibility of fungal endophthalmitis, intraocular corticosteroids should probably be avoided. Otherwise, intravitreal corticosteroids may be considered at the treating physician's discretion.

Prognosis

Visual prognosis is highly dependent on the virulence of the organism. Coagulase-negative *Staphylococcus* species and culture-negative endophthalmitis tend to have better visual prognoses [30]. In acute postoperative endophthalmitis, where coagulase-negative *Staphylococcus* is the predominant organism, the EVS showed that patients regained visual acuities of 20/40 or better 50 % of the time, while only 15 % had outcomes of 20/200 or worse [7]. Delayed-onset postoperative endophthalmitis after cataract surgery is also associated with less virulent organisms, and it tends to have better visual prognosis [8]. Delayed-onset bleb-associated endophthalmitis, on the other hand, is associated with much worse visual prognoses due to the higher virulence of organisms, with *Streptococcus* species being the most prevalent organism. Up to 1/3 of patients had final visual outcomes of NLP in one study [5, 27]. In posttraumatic endophthalmitis, visual acuity outcomes are also highly dependent on organism, but in general visual prognosis is guarded. The presence of an intraocular foreign body in endophthalmitis portends a worse prognosis, with 50 % of patients achieving visual outcomes of hand motions or worse [31]. Post-injection endophthalmitis visual outcomes also tend to be worse than outcomes after acute postoperative endophthalmitis due to the higher prevalence of *Streptococcus* species in the post-injection eyes [32].

Specific Considerations in Exogenous Endophthalmitis

Acute Postoperative Endophthalmitis

Acute postoperative endophthalmitis presents less than 6 weeks after eye surgery, by definition [8]. The most common causative surgery is cataract surgery, but other eye surgeries can also cause endophthalmitis, including penetrating keratoplasty, trabeculectomy, glaucoma drainage device implantation, pars plana vitrectomy, and scleral buckle [1].

Acute postoperative endophthalmitis can often be distinguished from a noninfectious inflammatory syndrome called toxic anterior segment syndrome (TASS), which may also occur acutely after intraocular surgery [33]. TASS is thought to be related to instillation of inflammatory agents (such as residues, preservatives, denatured medications, etc.) into the eye during surgery [16, 33]. TASS usually presents in the hyperacute phase after surgery, often in the 12–48 h period. The distinguishing features of TASS are diffuse limbus-to-limbus corneal edema, severe anterior chamber reaction but minimal vitritis, and minimal ocular pain on presentation. However, it can be difficult to distinguish TASS from endophthalmitis in some cases, and these patients often must be presumed to have bacterial endophthalmitis.

Preoperative risk factors for acute postoperative endophthalmitis include blepharitis, immunosuppression (including diabetes mellitus), and older age [1, 34]. Intra- and postoperative risk factors include intraoperative complications, particularly posterior capsular rupture with vitreous loss, inexperienced surgeons, and postoperative wound leak [35]. Injection of prophylactic intracameral antibiotics, use of acrylic intraocular lenses (versus silicon), and use of scleral tunnel (versus clear corneal incision) have been shown to be protective against endophthalmitis in some studies, although these associations have been debated [1, 36].

Acute postoperative endophthalmitis is nearly always caused by a bacterial infection, although acute postoperative fungal endophthalmitis is a prevalent complication in developing countries [1]. Vitreous cultures may be negative in up to 30 % of cases [1, 13]. Of culture-positive cases, the most common organisms found are gram-positive cocci. Of these, coagulase-negative *Staphylococcus* is most common, followed by *Staphylococcus aureus* and then *Streptococcus* species [7, 13, 14, 18].

Chronic Postoperative Endophthalmitis

Delayed-onset or chronic postoperative endophthalmitis presents later than 6 weeks after surgery [8]. Diagnosis may sometimes be further delayed, because of the insidious onset of these cases. Delayed-onset postoperative endophthalmitis is relatively uncommon, accounting for less than 8 % of all postoperative endophthalmitis cases in one study [37]. Patients often present with remitting and relapsing intraocular inflammation, many times without a frank hypopyon. Patients often do not have

pain or redness on presentation. The characteristic finding of chronic postoperative endophthalmitis is a white plaque within the lens capsule, which is a nidus of the infection [8].

Vitreous or aqueous cultures in these cases are often negative. Of culture-positive cases, the most common causative organism is *Propionibacterium acnes*, followed by coagulase-negative *Staphylococcus* species. Fungal infections may also be a cause of delayed-onset endophthalmitis, accounting for up to 25 % of these cases [1, 8].

Treatment of chronic bacterial endophthalmitis can sometimes be challenging. Although simple injection with antibacterial antibiotics may be curative in some cases, often the infection is not completely eradicated with intravitreal injection alone. Pars plana vitrectomy with partial capsulectomy and intravitreal antibiotic injection can increase the rate of cure; however, some patients will still go on to harbor persistent infection. The definitive procedure in these patients is pars plana vitrectomy with complete removal of the intraocular implant and lens capsule with injection of intravitreal antibiotics, but this procedure should be reserved for recurrent cases, as the patients will typically later need an additional operation to insert a secondary intraocular lens implant [38].

Bleb-Associated Endophthalmitis

Trabeculectomy is associated with a particular subset of exogenous endophthalmitis, referred to as *bleb-associated endophthalmitis*. Onset can be acute or delayed, often many months or years after the initial surgery [22]. Acute-onset bleb-associated endophthalmitis is similar to other forms of acute postoperative endophthalmitis, as described above, but delayed-onset bleb-associated endophthalmitis can be associated with more virulent bacteria with more guarded visual prognosis (Fig. 6.2). *Streptococcus* species and gram-negative bacteria such as *Haemophilus influenzae* are the most common organisms causing delayed-onset bleb-associated endophthalmitis [5, 27].

Bleb-associated endophthalmitis must be distinguished from blebitis, which may often be treated with topical antibacterial antibiotics alone [22]. Both bleb-associated endophthalmitis and blebitis often present with a purulent filtering bleb and anterior ocular inflammation, but blebitis presents with little vitritis and no hypopyon. Despite proper treatment, blebitis may still develop into bleb-associated endophthalmitis; therefore these patients must be monitored closely.

Risk factors for bleb-associated intraocular infections include a history of previous blebitis, late-onset bleb leak, younger age, antimetabolite use during surgery, inferior blebs, thin avascular blebs, myopia, and blepharitis. Fornix-based trabeculectomy surgery may be associated with less risk than limbus-based surgery, but this has been debated [1, 39].

Because of the association of delayed-onset bleb-associated endophthalmitis with more virulent organisms, more aggressive management of this disease, including urgent PPV, should be considered [27]. During the operation, the surgeon may

consider injecting antibiotic subconjunctivally around the bleb in addition to intravitreally, to help with clearance of the inciting bleb infection.

Post-injection Endophthalmitis

Intravitreal injections, the most common of which are anti-vascular endothelial growth factor (anti-VEGF) medication injections, are routinely given for the treatment of a variety of retinal conditions including diabetic macular edema, age-related macular degeneration, and macular edema secondary to retinal vein occlusion. Although the risk of endophthalmitis with this treatment is low (0.02–0.32 %) [15], because intravitreal injections are becoming more and more common, the incidence of post-injection endophthalmitis has risen dramatically in the past 10 years. Incidence of endophthalmitis may be higher with injection of intravitreal triamcinolone acetonide than with other intravitreal medications, although this may be related to higher incidence of sterile endophthalmitis with triamcinolone [40].

Sterile or noninfectious endophthalmitis can occur after intravitreal injection and has been reported after injection of aflibercept, bevacizumab, ranibizumab, and triamcinolone [1]. It may be related to an immune response to the medication itself, or in the case of triamcinolone, it may be related to migration of small medication particles into the anterior chamber of the eye [41]. Usually, sterile endophthalmitis presents with minimal pain, less inflammation, and more acute presentation than bacterial endophthalmitis, but distinction between noninfectious and infectious endophthalmitis can be difficult, and it is often prudent to treat these cases as infectious.

Risk factors for post-injection endophthalmitis may include older age, diabetes mellitus, blepharitis, subconjunctival anesthesia, patient moving/squeezing during the injection, use of prophylactic antibiotic eye drops, and use of a conjunctival mold, although it is challenging to find definitive risk factors given the low incidence of the disease and lack of prospective studies [4, 42]. The use of compounded medications for intravitreal injection has also been a recent topic of debate, as there have been several outbreaks of bacterial and fungal endophthalmitis related to contaminated batches of compounded bevacizumab and triamcinolone [43, 44]. However, with proper sterile compounding techniques, the dreaded occurrence of a batch-related endophthalmitis outbreak can be avoided.

Similar to postoperative endophthalmitis, organisms associated with post-injection endophthalmitis are nearly always gram-positive cocci [4, 42]. Coagulase-negative *Staphylococcus* species are most common, followed by *Streptococcus* species and then *Staphylococcus aureus* [4, 42]. However, infection with *Streptococcus* species is up to three times more common in post-injection endophthalmitis versus postoperative endophthalmitis, suggesting there may be increased incidence of contamination of the injection site with oral flora in these cases [32].

Posttraumatic Endophthalmitis

Posttraumatic bacterial endophthalmitis is a rare type of exogenous endophthalmitis but can be associated with the most virulent and varied organisms. Endophthalmitis occurrence after open globe trauma ranges from 2 to 12 % [1, 11, 45, 46]; percentages may be as high as 50 % with intraocular foreign body [11], although this percentage is highly variable depending on geographic region and mechanism of injury [45, 47]. Risk factors include presence of an intraocular foreign body, injury with dirty or plant material, traumatic lens rupture, corneal wound, retinal break/detachment, long hospital stay, rural location, and delayed wound closure [11].

In addition to the typical presenting signs of endophthalmitis, posttraumatic endophthalmitis may be associated with retained foreign bodies that are either partially embedded in the cornea or sclera, or intraocular foreign bodies (IOFB), or, if there is a perforating injury, there can be intraorbital or intracranial foreign bodies. Additional orbital and/or brain imaging is warranted via ultrasound, plain radiography, or CT scan to evaluate for the presence and location of a foreign body if suspected, as it may help determine surgical approach for removal of the foreign body [11, 48, 49]. Of note, some metallic foreign bodies, particularly 100 % copper ones, can cause sterile inflammation including hypopyon and vitritis, which may be difficult to differentiate from infectious endophthalmitis [11].

Most (80–90 %) of culture-positive cases of posttraumatic endophthalmitis are caused by bacteria, but the incidence of fungal endophthalmitis is higher than with other mechanisms of exogenous endophthalmitis [50]. Gram-positive cocci are the most common bacterial isolates, followed by gram-positive bacilli (e.g., *Bacillus cereus*) and then gram-negative organisms [50, 51]. Among gram-positive cocci, coagulase-negative *Staphylococcus* species and *Streptococcus* species are the predominant groups. The gram-positive *Bacillus cereus* is particularly devastating to the eye and is a common causative organism of endophthalmitis after trauma. *B. cereus* is often associated with a hyperacute presentation and fulminant bacterial endophthalmitis, and infection with this organism has extremely guarded visual prognosis [11, 52]. *Enterobacter* and *Pseudomonas*es are the most common gram-negative pathogens in a traumatic setting and also portend a poor visual prognosis [1, 11, 53].

Candida species are the most prevalent fungal infections after trauma, but infection with *Aspergillus* and *Fusarium* species is also common [23, 50]. Clinical features suggestive of fungal infection include delayed onset of infection, usually between 1 and 5 weeks after injury, or unresponsiveness to standard antibacterial antibiotics. Clinical signs suggestive of fungal endophthalmitis include minimal pain and minimal conjunctival redness or chemosis on presentation, slowly progressive intraocular inflammation, and the presence of inflammatory infiltrates in the vitreous or anterior chamber that resemble “fluff balls,” “snowballs,” or a “string of pearls” [1, 11]. Infections with yeast (e.g., *Candida*) are more indolent than infections with molds (e.g., *Aspergillus*) and portend better visual prognoses [23].

Endogenous Endophthalmitis

Endogenous endophthalmitis is an uncommon form of endophthalmitis, accounting for about 5 to 10% of all endophthalmitis cases [1]. It is due to hematogenous spread of infection to the eye and is nearly always caused by bacterial or fungal infection (Figs. 6.3 and 6.4). There is a high prevalence of systemic comorbid illnesses and factors in patients who present with endogenous endophthalmitis, including uncontrolled diabetes mellitus, malignancies, intravenous drug use, organ abscess, immunosuppressive therapy, indwelling catheter, end-stage renal or liver disease, and endocarditis [1, 24, 54, 55]. However, some patients have no predisposing factors, and rarely no source of infection is found [55].

Unlike in exogenous endophthalmitis, fungal infection is more prevalent than bacterial infection in many series of endogenous endophthalmitis [54, 56, 57]. The most common type of fungal infection is by *Candida* species, followed by *Aspergillus* (Fig. 6.5) [24, 58]. Mold species such as *Aspergillus* are more commonly associated with systemic immunosuppression and organ transplantation, and signs of endophthalmitis manifest rapidly [59]. Endogenous *Candida* endophthalmitis is often more indolent and presentation can be delayed; misdiagnosis in these cases is common [60]. *Candida* may start as choroidal lesions with minimal vitreous involvement, and these early candidal infections may resolve with systemic antifungal medications alone [61].

Endogenous bacterial endophthalmitis is usually due to gram-positive bacteria such as *Staphylococcus* (usually *S. aureus*) and *Streptococcus* species (e.g., *S. pneumoniae*, *Group B Streptococcus*, *Enterococcus*) in the Western world [2, 57]. However, in Asian countries, gram-negative species, particularly *Klebsiella* species, are the most common cause of endogenous bacterial endophthalmitis, and prevalence of gram-negative infections is also increasing in Western countries [3, 54, 56].

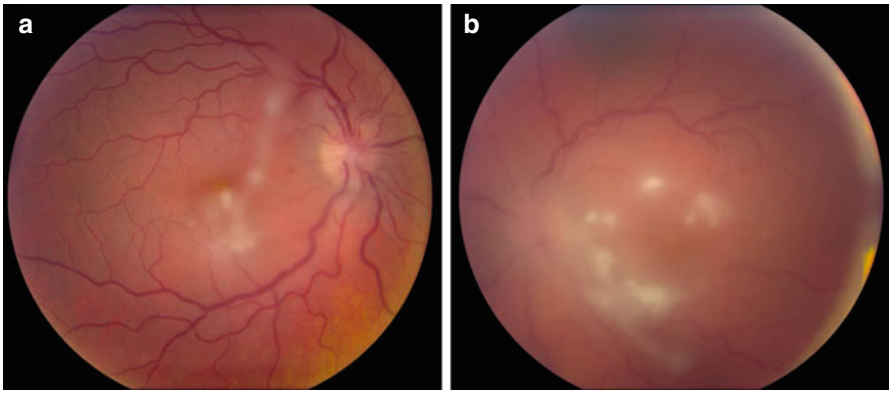

Fig. 6.5 Endogenous fungal endophthalmitis. Infection was due to *Candida albicans*, introduced into the bloodstream via intravenous heroin abuse. (**a**, **b**) There was moderate vitritis in the right eye and severe vitritis in the left eye, with multifocal fluffy vitreous balls of inflammation. In the right eye, the vitritis appeared to emanate from a fluffy chorioretinal lesion in the posterior pole, just inferior to the macula

In these cases, liver abscess is typically the source of infection. In a series from a major Taiwanese hospital, nearly 2/3 of all endogenous endophthalmitis patients had liver abscesses, and most of these patients had *Klebsiella* endophthalmitis [56].

Nocardia endophthalmitis is typically seen in patients with underlying immunosuppression, although it may also occur in otherwise healthy individuals [9, 62]. It is commonly associated with pulmonary infection, although ocular symptoms are often the presenting complaints [63].

Presentation

The presenting ocular symptoms and signs are similar to exogenous endophthalmitis, as discussed above. Symptoms can vary from patient to patient, with some having more indolent presentation if less pathogenic organisms are involved or more acute presentations if highly virulent pathogens are the culprit. However, since the pathogenesis involves the hematogenous spread of infection to the eye from another source, often there may also be systemic signs and symptoms, with fever and flu-like symptoms being most common and occurring in approximately 1/3 of patients. In fact, nearly 75 % of patients have some form of preceding or accompanying sign of systemic infection [3, 54]. In addition, because of the hematogenous spread of the infection, bilateral involvement can occur in up to 1/3 of cases [1, 3, 54]. Diagnosis of endogenous endophthalmitis may be difficult, as there is often no inciting illness noted by history. Up to 25 % of cases were misdiagnosed or had a delayed diagnosis in one study [3].

Also, because endogenous infections spread from the choroid, intraocular infections may only involve the choroid or subretinal space without causing fulminant endophthalmitis (Fig. 6.6) [9, 58, 63]. Subretinal abscess is an uncommon manifestation of

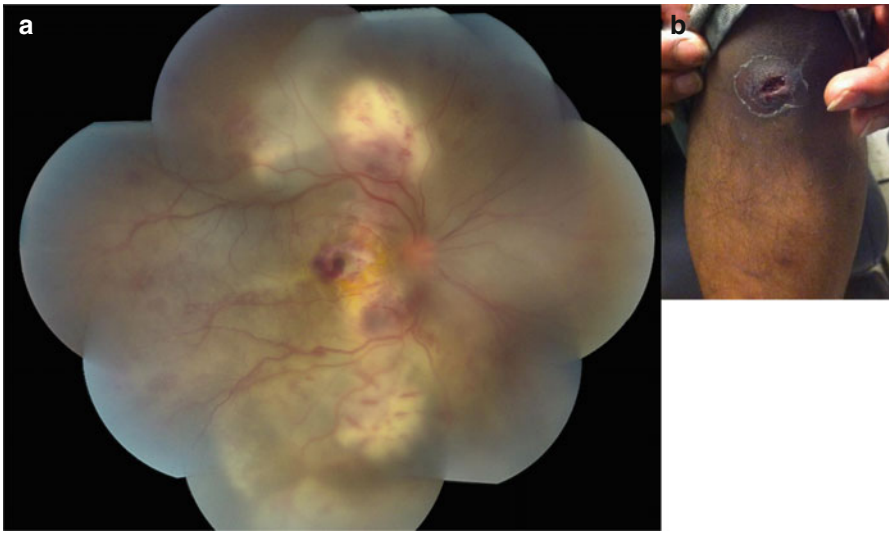

Fig. 6.6 Subretinal abscess. Infection was to methicillin-sensitive *Staphylococcus aureus* introduced into the bloodstream via a skin abscess. (**a**) Examination revealed moderate vitritis and a large multilobular subretinal white mass with overlying exudative retinal detachment, as well as multiple white-centered intraretinal hemorrhages. (**b**) An open skin wound

endogenous endophthalmitis. Subretinal abscesses usually appear in the posterior fundus as yellow-white circumscribed lesions, often with hemorrhages in the overlying retina, and mild to moderate vitreous inflammation. Subretinal pseudohypopyon and more extensive exudative detachment may occur in advanced cases [9]. *Nocardia* is the organism most commonly associated with these lesions, although other organisms may also cause subretinal abscess [9].

Diagnostic Testing

Diagnosis of the causative organism in endogenous endophthalmitis is often aided by vitreous biopsy, as blood cultures are negative in many of these cases. Blood cultures may only be positive 33–50 % of the time [3, 64], while vitreous biopsy may be positive in up to 87 % of patients [64]. In cases of fungal endophthalmitis or subretinal abscess, PPV with vitreous or subretinal fine needle biopsy may be particularly helpful to obtain adequate specimen for culture [9, 59]. Diagnosis of *Nocardia* can be particularly challenging, and a PPV with subretinal biopsy is often necessary to obtain an adequate sample for culture [63].

Additional systemic testing may be tailored to symptoms and suspected organisms. Management should be done in conjunction with an infectious disease expert. Blood and serological testing is often helpful to detect systemic disease. There may be a leukocytosis, with increased neutrophil count. Erythrocyte sedimentation rate and C-reactive protein, which are nonspecific tests of inflammation, are often elevated, particularly in cases of endocarditis. Other niduses of infection are common and can be found in a variety of extraocular tissues. Indwelling intravenous catheters may be removed and cultured. If there are signs of a urinary tract infection, urine cultures may be sent. Lung, liver, endocardium, and soft tissue were most commonly reported sites of primary infection in one study [2]. Therefore, lung, abdominal, and cardiac imaging, with radiography or echography or both, is important in many cases of endogenous endophthalmitis. To detect infection of the aortic valve, transesophageal ultrasound may be more sensitive than transthoracic ultrasound. In cases of gram-negative bacterial endogenous endophthalmitis, particularly in *Klebsiella* species infections, a liver abscess is often the primary infection site; therefore diagnostic imaging of the abdomen is often advisable in these cases [54]. Head and orbital imaging may be helpful in some cases.

Treatment

Treatment of endogenous endophthalmitis typically includes hospitalization and systemic intravenous antibacterial and/or antifungal medications, in addition to intravitreal antibiotic injections. Intravitreal medications and doses are identical to those used in exogenous endophthalmitis, as discussed above. Often it is prudent to inject antifungal medications in addition to antibacterial medications intravitreally if the causative organism is not known. Systemic medications are important in treatment of endogenous endophthalmitis, as there is typically an occult or manifest systemic infection in these cases [3].

In fungal endophthalmitis, instead of intravenous amphotericin B or other intravenous antifungal agents, oral fluconazole or voriconazole may be used in some

cases as an adjunctive therapy, as the ocular penetration is relatively good [59, 65]. Intravitreal amikacin and oral trimethoprim/sulfamethoxazole should be considered for treatment of intraocular *Nocardia* [63].

The role of therapeutic PPV is unclear in endogenous endophthalmitis, but as in cases of exogenous endophthalmitis, PPV should be considered in cases where more virulent organisms are suspected. In one large series of endogenous endophthalmitis, visual outcomes were better in patients who underwent PPV than in those who did not [3]. PPV may also be used to aid in obtaining a specimen for diagnosis.

Prognosis

Visual prognosis in these cases is guarded, due to the virulence of organisms typical of endogenous endophthalmitis. In one study, visual results were worse prior to 2001, when visual acuities of better than 20/200 were seen in only 1/3 of patients, while after 2001, up to 41 % of patients were able to obtain 20/200 or better vision [2, 3]. Up to 20 % of eyes needed enucleation or evisceration in the same study [3]. Of cases of endogenous fungal endophthalmitis, molds such as *Aspergillus* species portend the worst visual prognosis (up to 25 % enucleation rate), while yeasts such as *Candida* species are associated with the best visual prognoses [1, 59].

Atypical Bacteria

Tuberculosis

Tuberculosis (TB) is a disease caused by infection with *Mycobacterium tuberculosis*. It is a systemic disease that can have "protean manifestations" and mainly involves the lung [66]. Although most commonly found in the lung, the disease may manifest anywhere in the body; extrapulmonary sites may include the gastrointestinal tract, genitourinary tract, skin, central nervous system, and eye. In some cases, the organism can disseminate from the lungs by hematogenous spread to various organs resulting from seeding of tissues with small nodules of infection; this is termed miliary tuberculosis [66].

There is an annual incidence of approximately nine million cases per year, and TB is the cause of three million deaths yearly worldwide [66]. The disease is uncommon in the USA but is becoming increasingly more common in underdeveloped regions of the world. In the USA, immigrants and racial and ethnic minorities are most affected, with the most common groups being Asian immigrants. Most of the new cases of TB in the USA are due to reactivation of latent TB in HIV-infected individuals [67].

Presentation

Mycobacterium tuberculosis (TB) is an acid-fast bacillus that spreads via airborne droplets, which can remain suspended in the air for a few hours. Over 90 % of people infected with TB never develop symptoms, 5 % develop the disease in the first

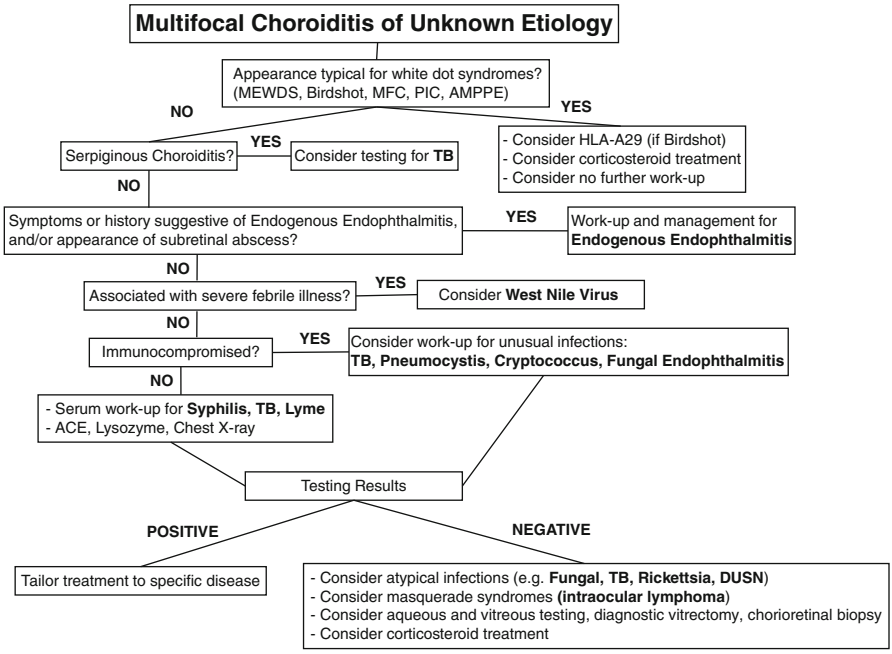

Fig. 6.7 Multifocal choroiditis of unknown etiology. *MEWDS* multiple evanescent white dot syndrome, *AMPPE* acute multifocal placoid posterior epitheliopathy, *PIC* punctate inner choroidopathy, *MFC* multifocal choroiditis, *TB* tuberculosis, *DUSN* diffuse unilateral subacute neuroretinitis

few years after infection, and the remaining 5 % develop symptoms later because of a weakened immune system. In this last group of patients, termed latent TB, most patients remain asymptomatic, but a few surviving dormant bacilli occasionally reactivate and can cause a wide variety of symptoms. There is no radiographic evidence of pulmonary involvement in latent TB [68].

TB is considered to be a "great masquerader," along with Lyme disease and syphilis, and can manifest in the eye as inflammation in a large variety of ocular structures. The most common ocular manifestations are posterior uveitis and panuveitis, and intraocular manifestations often also include choroidal granulomas (Figs. 6.7 and 6.8). Other presentations include subretinal abscess, serpiginous-like choroiditis, intermediate uveitis, and retinal vasculitis and/or vascular occlusion (Eales' disease) [68]. Anterior segment manifestations are less common, and appearance can include anterior uveitis, phlyctenulosis, episcleritis and scleritis, and peripheral ulcerative keratitis [67]. Of the anterior segment presentations, granulomatous anterior uveitis is most common and may be associated with anterior segment granulomas or nodules [66].

Choroidal granulomas are the most common manifestation of ocular TB and usually are found in conjunction with systemic TB infection, either pulmonary or extrapulmonary. They can be unifocal or multifocal, are white or yellow in color, and can

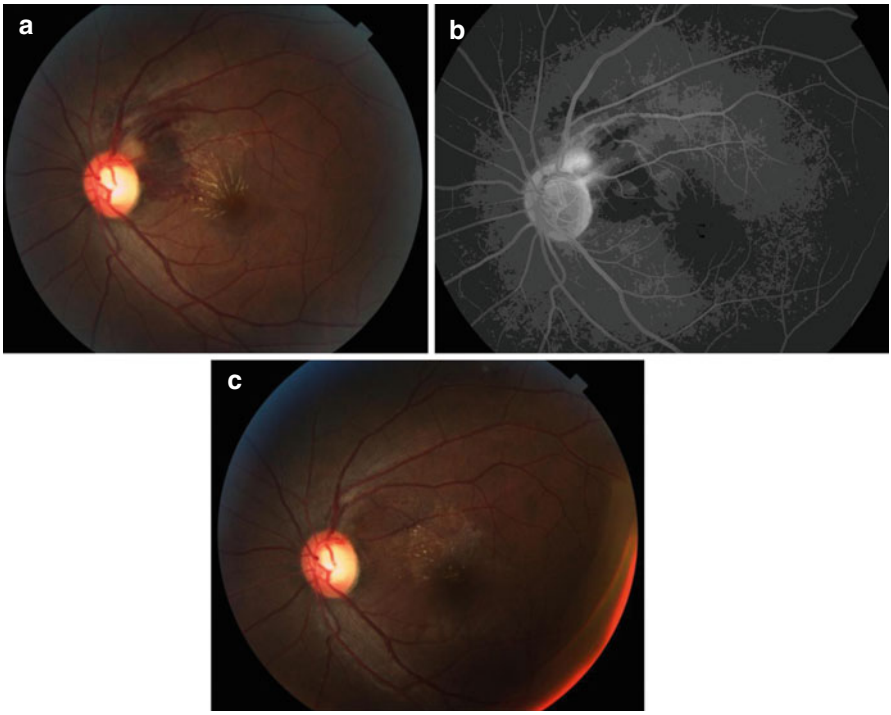

Fig. 6.8 Tuberculosis neuroretinitis. CT scan of the chest and positive interferon-gamma immunoassay confirmed presumed intraocular tuberculosis. (**a**) Granulomatous peripapillary chorioretinal lesion with surrounding subretinal hemorrhage and an associated partial macular star. (**b**) Fluorescein angiography showed early hyperfluorescence and late leakage from the granuloma and associated mild retinal vascular staining and leakage. (**c**) Visual acuity gradually returned to normal and retinal findings improved after 4 months of treatment

have overlying hemorrhage, exudate, or subretinal fluid [66]. Small granulomas are termed tubercles, and larger ones are termed tuberculomas [66]. If they enlarge further, a subretinal abscess may form.

Eales' disease is caused by periphlebitis, secondary retinal non-perfusion, and often leads to subsequent retinal neovascularization with vitreous hemorrhage or tractional retinal detachment. The precise mechanism is unknown but is thought to be due to hypersensitivity to an antigen of *Mycobacterium tuberculosis* [69].

Serpiginous-like choroiditis is a more recently recognized manifestation of TB. Like Eales' disease, serpiginous-like choroiditis may be related to hypersensitivity to a mycobacterial antigen and results in multifocal plaque-like choroiditis that may or may not be contiguous in the posterior pole. Distinguishing features from noninfectious serpiginous choroiditis may include associated vitritis, unilateral presentation, and sparing of the peripapillary region, but the two entities may be difficult to distinguish from each other, and testing for TB and subsequent response to TB treatment is often necessary to make the distinction.

Diagnostic Testing

Diagnosis of TB may be difficult due to the paucity and difficulty of obtaining organisms for culture or staining. To aid in diagnosis, tuberculin skin testing (TST) has long been used to assess for prior exposure to *Mycobacterium tuberculosis*. In this test, a small amount of mycobacterial antigen, or purified protein derivative (PPD), is injected subcutaneously. A positive TST appears as a raised reddish skin reaction at the site of injection.

One of the disadvantages of the TST is that the skin reaction is delayed, and the test must be read between 48–72 h after administration, which may delay diagnosis and requires patients to return to the clinic for reading. Additionally, results may be difficult to interpret in patients who have previously been exposed to the bacille Calmette–Guerin (BCG) vaccine, as this vaccine can produce false-positive skin testing results. More recently, T-cell interferon-gamma release assays have been developed, which have the advantage of permitting same-day results from a single blood serum sample and increased specificity for *Mycobacterium tuberculosis* which avoids false-positive results due to previous BCG vaccination [70].

If organisms can be obtained, and a patient has ocular manifestations of TB, the patient is said to have *confirmed* ocular TB. If no organism specimen is obtained but the patient has ocular manifestations along with positive testing for TB which may include tuberculin skin testing, positive interferon-gamma serum testing, a lesion on chest radiography consistent with TB, or extrapulmonary imaging consistent with TB, then the patient is said to have *presumed* ocular TB [68]. The disadvantage of relying on a positive TST or interferon-gamma serum assay is that these tests cannot distinguish between latent and active tuberculosis infection [67]. In these cases, mycobacterium DNA may sometimes be obtained by sampling of the ocular fluid, which may then be sent for PCR assay. However, the yield of ocular fluid biopsy and PCR testing is low in TB; therefore routine ocular fluid sampling is not warranted in most cases of presumed ocular TB [66, 67].

Treatment

The management of ocular tuberculosis is complex, even more so in the era of multidrug-resistant TB. Management should be done in conjunction with an infectious disease expert. Treatment of ocular TB is the same as treatment for pulmonary or extrapulmonary TB [71]. In general, the Centers for Disease Control (CDC) recommends use of the four common anti-TB drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) for an initial 2-month period followed by a choice of different options over the next 4–7 months for treatment of tuberculosis. Usually, pyrazinamide and ethambutol are stopped, and isoniazid and rifampin are continued to complete a 9–12-month treatment course, although recommendations vary [66].

Corticosteroids may be used in conjunction with the anti-TB therapy but should not be used alone when treating ocular TB. If a patient has inflammatory uveitis unrelated to TB, but also has latent TB (a positive TST or interferon-gamma assay), corticosteroids or immunomodulators may be given but only in conjunction with isoniazid or rifampin monotherapy for a full treatment course for latent TB [66].

Syphilis

Syphilis, infection by the spirochete *Treponema pallidum*, is another rare but important cause of intraocular infection and secondary uveitis. It is spread by sexual contact, transplacentally to the fetus, or rarely by blood transfusion [68]. There are three clinical stages of syphilis. In primary syphilis, a painless chancre is often observed at the site of inoculation, which disappears spontaneously over 4–6 weeks. Secondary syphilis may then follow, presenting with fever, malaise, and mucocutaneous lesions. This is the most infectious stage of syphilis, and ocular involvement occurs in up to 10 % of cases. Tertiary syphilis occurs later, months or years after primary infection, and is characterized by gummas, which are soft, tumor-like nodules of inflammation. Latent syphilis may also occur, which implies seropositivity but no symptoms of active disease. Neurosyphilis can occur at any stage and is classified as early or late [68].

Rates of syphilis in the developed world, including the USA, have been increasing over the past two decades, probably due to an increase in unprotected sex in the era of antiretroviral therapy for the human immunodeficiency virus (HIV) [72]. In the USA, the rate of primary and secondary syphilis in 2013 was more than double that in 2000. Young men account for the majority of cases in the USA, and men having sex with men represents the highest risk group [73]. Tertiary syphilis is the most common presentation of the disease, representing over 2/3 of cases in the USA in 2012 [74]. In the current era, coinfection with HIV is common, occurring in approximately 1/2 of newly diagnosed syphilis cases [74]. Therefore, if a new diagnosis of syphilis is made, additional testing for HIV infection is crucial.

Presentation

Like tuberculosis, ocular syphilis is a "great masquerader," as it can present with inflammation in any part of the eye and can have a large variety of appearances. Syphilitic uveitis usually presents with granulomatous inflammation and can present as nonspecific anterior, intermediate, or posterior uveitis or as panuveitis, episcleritis/scleritis, or keratitis. Posterior manifestations are most common and include vitreous inflammation, chorioretinitis, retinal vasculitis, serous retinal detachment, and, rarely, necrotizing retinitis. Optic nerve manifestations include inflammatory disk edema, neuroretinitis, pallor, or optic nerve nodules (gummas). Because of the variety of presentations, testing for syphilis infection should be considered for many cases of chronic uveitis.

There are distinctive appearances of retinal infection that can assist in rapid diagnosis of syphilitic uveitis. The first is the presence of superficial retinal precipitates in panuveitis [75]. The precipitates are small and creamy and can migrate over the infected regions of retina. Retinitis caused by syphilis has a mildly opacified appearance, which is often distinct from the typical chalky white appearance of necrotizing retinitis seen with viral infections (Figs. 6.9 and 6.10). One of the other features of syphilitic retinitis is that it leaves behind minimal disruption of the retinal pigment epithelium when it heals [75].

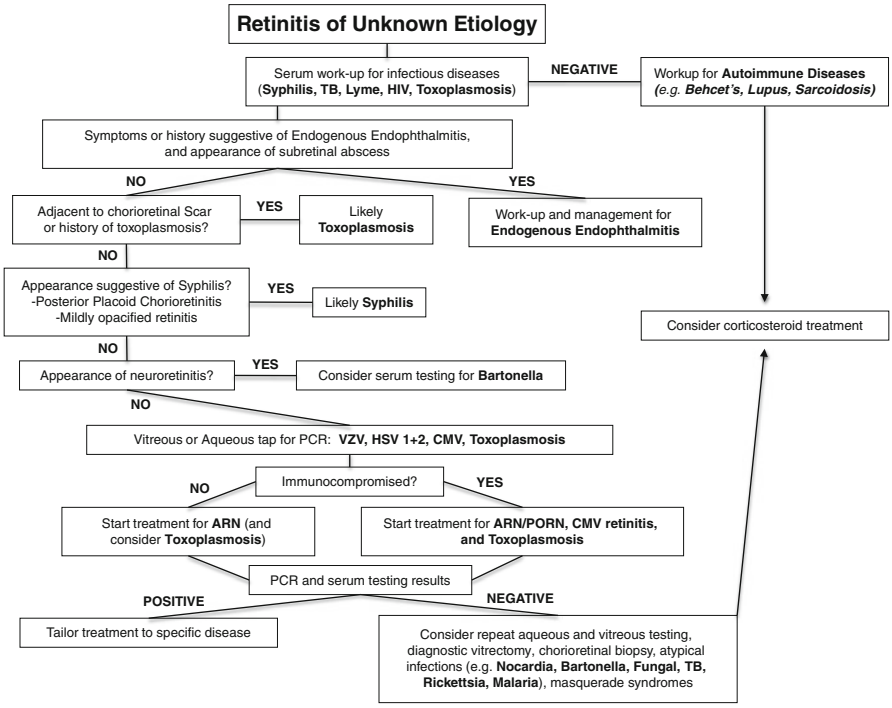

Fig. 6.9 Retinitis of unknown etiology. *TB* tuberculosis, *HIV* human immunodeficiency virus, *PCR* polymerase chain reaction, *HSV* herpes simplex virus, *VZV* varicella zoster virus, *CMV* cytomegalovirus, *ARN* acute retinal necrosis, *PORN* progressive outer retinal necrosis

Another distinctive pattern is that of acute syphilitic posterior placoid chorioretinitis [76, 77]. This appears as a discrete nummular area of outer retinal and inner choroidal inflammation in the posterior pole (Fig. 6.11). The lesion is gray-white or pale yellow, with evidence of central fading and a coarsely stippled hyperpigmentation pattern [77].

Congenital or latent syphilis can produce ophthalmic abnormalities such as optic neuropathies or pseudoretinitis pigmentosa but may not have active evidence of clinical disease and should be considered in patients with an appearance of unexplained optic neuropathy or retinal pigmentary changes with visual loss [74].

Diagnostic Testing

Clinical appearance can be further defined with multimodal retinal imaging, including fluorescein angiography (FA), indocyanine green angiography (ICGA), fundus autofluorescence, and optical coherence tomography [74]. In particular, posterior placoid chorioretinitis has the characteristic appearance of early and late hypofluorescence on ICGA, stippled hyperautofluorescence, and small amounts of subretinal fluid on OCT [76, 78].

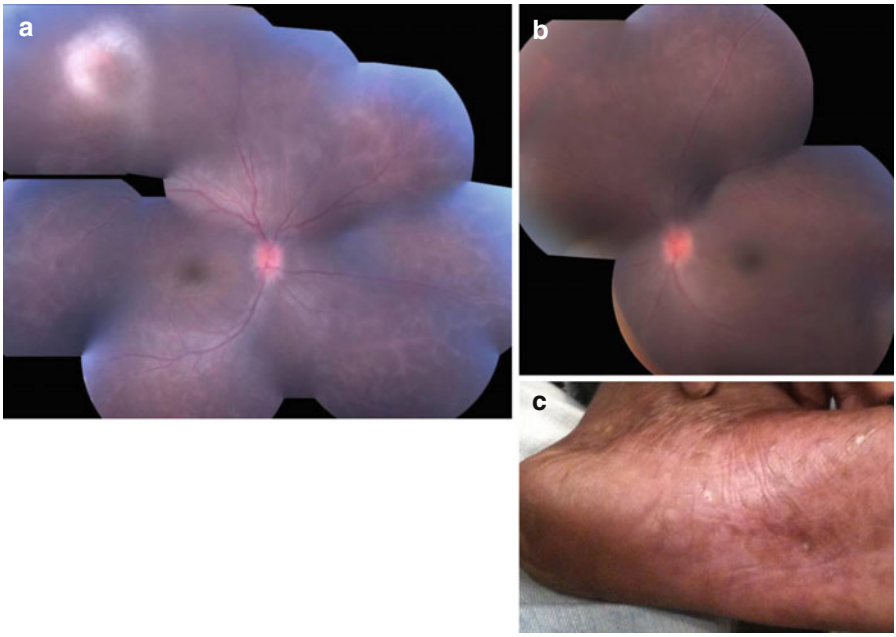

Fig. 6.10 Syphilitic retinitis. Diagnosis confirmed with serologic testing. (**a**, **b**) Vitritis and diffuse retinal vascular sheathing in both eyes. In the right eye, there was a patch of peripheral nummular and grayish-colored retinitis. The optic disks were mildly elevated and edematous. (**c**) Further review of systems revealed a maculopapular rash on the soles of both feet

Serologic testing is the standard for diagnosis of syphilitic uveitis. Seronegativity is rare but can occasionally occur, most commonly in HIV-positive patients. Commonly, two categories of tests may be ordered: treponemal and nontreponemal tests. The CDC currently recommends enzyme immunoassays and chemoluminescent immunoassays as the primary screening tests for syphilis to detect antibodies to treponemal antigens, followed by reflex testing of positive specimens with a nontreponemal test: the rapid plasma reagin (RPR) or the Venereal Disease Research Laboratory test (VDRL) [74].

The reason for this sequence of testing is that some patients will be positive by treponemal-specific tests but negative by RPR/VDRL. Because sensitivity of the treponemal-specific tests is higher than RPR/VDRL and specificity is lower, discordant results are expected. Specimens positive by treponemal-specific tests and negative on RPR/VDRL are submitted for a confirmatory *Treponema pallidum* particle agglutination test (TP-PA), and if that test is positive, a diagnosis of syphilis is confirmed [74]. Once a diagnosis of syphilis is made, the nontreponemal tests (RPR or VDRL) are useful to monitor response to treatment.

Patients with a new diagnosis of syphilitic uveitis should also have examination of the cerebrospinal fluid. Patients who have a prior diagnosis of syphilis as well as

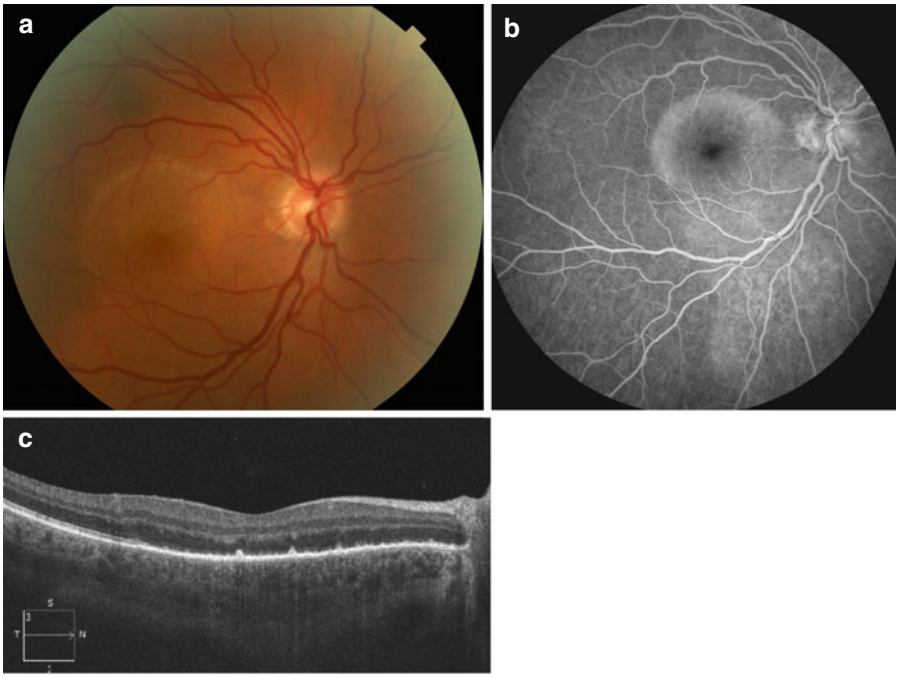

Fig. 6.11 Acute syphilitic posterior placoid chorioretinitis. Diagnosis confirmed with serologic testing and histopathology of skin lesion. (**a**) A discrete nummular area of outer retinal and inner choroidal inflammation in the posterior pole is evident. (**b**) Fluorescein angiography reveals early hyperfluorescence with late leakage in the region of retinitis. (**c**) Optical coherence tomography reveals irregularities of the retinal pigment epithelium and disruptions of the ellipsoid zone

new unexplained ophthalmic abnormalities also warrant further investigation with examination of the cerebrospinal fluid [79]. VDRL is less sensitive than treponema-specific testing in the cerebrospinal fluid. Occasionally, only leukocytosis or elevated protein is present in neurosyphilis [74].

Treatment

Ocular syphilis is typically considered secondary syphilis as well as neurologic syphilis. It is treated in the same manner as neurosyphilis according to CDC guidelines. Subsequent fourfold decrease in titer by the nontreponemal test (RPR or VDRL) is evidence of a response to treatment [79]. Treatment should be given with guidance of an infectious disease specialist.

Intravenous or intramuscular penicillin is the drug of choice for ocular syphilis. The recommended adult regimen is intravenous penicillin G administered either in q4 hour doses or by continuous infusion for 10–14 days. The alternative regimen, if access to therapy can be ensured, is procaine penicillin intramuscularly once daily plus oral probenecid four times a day, both for 10–14 days. An extended course of benzathine penicillin intramuscularly once per week for up to 3 weeks

can be considered to provide longer duration of therapy [74]. Generally, the inflammation subsides with penicillin treatment with visual improvement within 1 month [78].

Oral corticosteroid may be used to decrease ocular inflammation and to avoid the Jarisch–Herxheimer reaction, a febrile inflammatory reaction caused by release of antigens from lysis of *Treponema pallidum* or other infectious organisms after initiation of treatment. Corticosteroids should only be given after systemic antibiotic treatment has been initiated [80].

Lyme Disease

Lyme disease is an arthropod-borne zoonosis prevalent in North America and Europe and is transmitted by the Ixodes tick. Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi* in the USA, but other forms of *Borrelia* may cause the disease in European countries [81]. As in syphilis, there are three clinical stages of Lyme disease. Stage one occurs between 1 and 4 weeks after inoculation and is typified by an expanding circular rash (erythema migrans) and nonspecific flu-like symptoms. Stage 2 occurs after 4 weeks and involves hematogenous dissemination of the infection to other parts of the body. Symptoms can be varied but may include more diffuse skin rash, neurologic symptoms, arthritis, and/or carditis [81]. Stage 3 may occur months or years after initial infection and often is associated with central nervous system manifestations. Ocular manifestations are most common in stage 2 or 3 of the disease [82].

Incidence of Lyme disease in the USA has been increasing since national surveillance was instituted in 1991. Lyme disease is regional, with most cases occurring in New England and the mid-Atlantic states and less commonly in parts of the Northern Midwest and Pacific states. The natural reservoirs for *B. burgdorferi* are small mammals and birds. Deer are not competent hosts for the spirochete but are important in sustaining the life cycle of the Ixodes ticks. Because of the mode of transmission, spring and summer months are the most common times for primary infection with *Borrelia* [81].

Presentation

As with syphilis, ocular manifestations of infection with *Borrelia burgdorferi* can be highly variable. The most common manifestation in the eye is conjunctivitis, which is usually self-limited and often does not represent true infection but is rather part of a flu-like syndrome in the first or early second stage of the disease [83]. As part of ocular infection, anterior manifestations may include keratitis, scleritis/episcleritis, and anterior uveitis. Intermediate uveitis is the most common form of uveitis associated with Lyme disease. Posterior involvement commonly may include macular edema, retinal vasculitis, and papillopathy and less commonly retinal venular occlusions or multifocal chorioretinitis [84]. In cases of optic neuritis, concomitant presence of cranial nerve palsies is common (mostly VI or VII) [82].

Diagnostic Testing
Serologic testing for Lyme disease is typically performed to confirm the diagnosis of ocular Lyme. Two-tier serologic testing for antibodies to *B. burgdorferi* is recommended. A quantitative test, usually an enzyme-linked immunosorbent assay [ELISA] of the concentration of antibodies to *B. burgdorferi*, is first performed, and if results are positive or equivocal, a Western blot is performed. Testing is often falsely negative in primary infection; therefore presence of the classic rash of erythema migrans may alone be diagnostic in early cases. The sensitivity of two-tier testing is much better in patients either with second- or third-stage Lyme disease (80–100 %). Although tests for antibodies have good sensitivity and specificity in patients who have had untreated infection for a month or longer, these tests should not be used for screening persons with a low probability of infection because of the poor positive predictive value in such patients [85].

Treatment
Treatment often involves a 2- to 4-week course of systemic antibiotics and should be guided by an infectious disease specialist. Early manifestations of Lyme may be treated with a course of oral doxycycline, amoxicillin, or cefuroxime, while late or neurologic Lyme may require intravenous administration of ceftriaxone or cefotaxime. Rates of cure with oral agents alone are in the 90 % range [81]. About 15 % of patients have a reaction similar to the Jarisch–Herxheimer reaction (increased temperature, myalgia, and arthralgia) within 24 h after treatment is begun with any of the above antimicrobial agents, as a result of an increase in circulating toxins associated with lysis of spirochetes [85].

Cat Scratch Disease

Cat scratch disease is prevalent worldwide and is a zoonosis caused by infection by *Bartonella henselae. Bartonella* are small gram-negative rods and are facultative intracellular bacteria within the class *Proteobacteria* [86]. The primary host reservoir for *B. henselae* is the domestic cat; more than 90 % of all cases of cat scratch disease are associated with a history of contact with cats less than 1 year old [87]. Infection of cats with *B. henselae* is common, but the transmission of the infection to humans is rare [88]. The cat flea, *Ctenocephalides felis*, has been established as the transmission vector from cat to cat and is thought to be a possible human vector as well [88].

Presentation
In most cases, cat scratch disease is a benign and self-limited condition. A localized skin lesion is usually seen at the inoculation site, sometimes accompanied by mild flu-like symptoms. These symptoms are typically followed by regional lymphadenopathy that will slowly resolve over weeks to months. Ocular involvement has been estimated to occur in up to 10 % of patients with cat scratch disease [89].

The most common ocular complication of cat scratch disease is Parinaud's oculoglandular syndrome, a self-limited condition typified by follicular conjunctivitis, regional lymphadenopathy, and fever. Posterior segment manifestations of cat scratch disease include neuroretinitis, focal retinitis, focal choroiditis, multifocal retinitis or choroiditis, vasculitis, intermediate uveitis, and vascular occlusions. Though only 1–2 % of patients infected with *B. henselae* develop neuroretinitis, among all patients with neuroretinitis, nearly two-thirds are seropositive for *B. henselae*, making cat scratch disease the most common cause of this condition. Neuroretinitis is typified by unilateral optic nerve head swelling with an associated exudative macular response, often in the pattern of a macular star (Fig. 6.8). Most patients with focal retinochoroiditis or neuroretinitis will have some degree of vitreous and/or anterior chamber inflammation [88].

Diagnostic Testing

Serologic testing is commonly used in the diagnosis of cat scratch disease. Culture or PCR-based analysis of tissue and/or fluid samples is uncommon but can occasionally be of use. There are two different serologic tests for the diagnosis of cat scratch disease. One involves an indirect immunofluorescent assay for the detection of serum anti-*B. henselae* antibodies. Sensitivity and specificity of this test are high in immunocompetent patients. The other is an ELISA directed toward serum antibodies, but this test is more variable in sensitivity and specificity, resulting in greater false-negative reporting [88].

Treatment

Cat scratch disease is often self-limited, so antibiotics are generally reserved for only the most severe infections. Immunocompromised patients affected with cat scratch disease tend to have a more protracted course and often require antibiotics. The most commonly used antibiotics are oral erythromycin or doxycycline. Doxycycline is typically preferred over erythromycin due to greater intraocular penetration. Both medications can be given intravenously or combined with oral rifampin in more severe infections. The duration of treatment is usually 2–4 weeks for immunocompetent patients and up to 4 months for immunocompromised patients [88].

Rickettsioses

Rickettsioses are a group of arthropod-borne zoonoses due to obligate intracellular small gram-negative bacteria. They are rare diseases, but intraocular involvement has been described. Most of them are transmitted to humans by the bite of contaminated ticks. Rickettsial agents are classified into three major categories: the spotted fever group, the typhus group, and scrub typhus. The spotted fever group includes Mediterranean spotted fever (MSF) and Rocky Mountain spotted fever (RMSF), among others. MSF is caused by the organism *Rickettsia conorii* and is prevalent in

Mediterranean countries and Central Asia. RMSF is caused by *Rickettsia rickettsii* and is endemic in parts of the Americas, especially in the South-Eastern and South-Central USA. Epidemic typhus is caused by the *Rickettsia prowazekii* and is usually found in crowded areas in populations with poor hygiene, such as during wars and natural disasters. Murine typhus, which is caused by *R. typhi*, is found worldwide in warm-climate countries. Scrub typhus, which is caused by *Orientia tsutsugamushi*, is found in East Asian countries [90–94]. See Table 6.2 for additional information on this unusual infection.

Whipple's Disease

Whipple's disease is a rare, multivisceral, and chronic infection typically presenting by a symptom triad of diarrhea, weight loss, and malabsorption. The digestive symptoms are often preceded for months or years by other symptoms, the most common being arthralgia, although cardiovascular, neurologic, or pulmonary involvement may be more prominent at times. Although the source of transmission is unknown, direct bacterial invasion has been found in numerous cases in various sites, including the eye. The bacteria *Tropheryma whipplei* most commonly invades the intestinal lamina propria and the vacuoles of "foamy" macrophages; less frequently, they are found in other intestinal mucosal structures, such as polymorphonuclear cells, smooth muscle, capillaries, lymphocytes, plasma cells, and mast cells. All of the clinical eye manifestations are nonspecific, including glaucoma, chemosis, retinal hemorrhage, papilledema, corneal ulcers, optic atrophy, and epiphora [95, 96]. Other patients have minimal intestinal symptoms with predominant ocular manifestations, leading to unfortunate delays in establishing a diagnosis. See Table 6.2 for additional information.

Viral Infections

Acute Retinal Necrosis

Acute retinal necrosis (ARN) is a rare and severe syndrome caused by intraocular infection by one of the herpes virus family. Although historically thought to affect otherwise healthy adults, more recently certain underlying immune characteristics, including certain human leukocyte antigen (HLA) subtypes, have been found that put patients at higher risk for the infection [97]. Immunosuppressive medications such as corticosteroids have been shown to predispose to infection [98]. Patients who are severely immunocompromised may present with a subtype of ARN called progressive outer retinal necrosis (PORN), described below.

The infectious agents associated with ARN and PORN are members of the herpes virus family. Varicella zoster virus (VZV) is most common, and most of the remaining cases are caused by infection by the herpes simplex virus (HSV)-1 or HSV-2.

Table 6.2 Unusual intraocular infections

Disease	Causative organisms	Epidemiology	Common history and symptoms	Ocular manifestations	Diagnostic testing	Treatment	Prognosis
Bacteria							
Rickettsioses	1. Mediterranean Spotted fever: *Rickettsia conorii* 2. Rocky Mountain Spotted fever: *Rickettsia rickettsii* 3. Epidemic typhus: *Rickettsia prowazekii* 4. Murine typhus: *Rickettsia typhi* 5. Scrub typhus: *Orientia tsutsugamushi*	1. Mediterranean countries and Central Asia 2. Parts of Americas, especially South-Eastern and South-Central USA 3. Crowded areas with poor hygiene 4. Worldwide in warm-climate countries 5. East Asia Transmitted to humans by tick bite	Present in spring or summer History of outdoor activities in endemic area Triad of high fever, headache, and general malaise Characteristic skin rash Local skin lesion (*tache noire*) at site of inoculation	Ocular involvement frequently asymptomatic and self-limited Retinitis common in MSF: perivascular white retinal lesions Multifocal deep retinitis seen in other forms of rickettsiosis Other retinal manifestations include serous retinal detachment, macular edema, macular exudates, and multifocal choroiditis Other ocular manifestations include optic disk edema, ischemic optic neuropathy, conjunctivitis, subretinal hemorrhage, keratitis, non-granulomatous anterior uveitis, and panuveitis	Typical clinical features can be diagnostic Usually confirmed by antibody testing of serum PCR may be useful	Drug of choice: doxycycline (oral or IV) Early systemic treatment advisable Other tetracyclines, chloramphenicol, fluoroquinolones also effective Consider systemic corticosteroids later	Usually good Severe cases may be lethal Ophthalmic manifestations usually self-limited Ocular involvement may cause permanent visual loss due to macular scarring or optic atrophy

(continued)

Table 6.2 (continued)

Disease	Causative organisms	Epidemiology	Common history and symptoms	Ocular manifestations	Diagnostic testing	Treatment	Prognosis
Whipple's disease	*Tropheryma whipplei*	Very rare Ubiquitous in environment, rarely cause of infection >75% in males Patients usually middle aged and Caucasian	Causes chronic and multisystemic involvement, including GI tract, CNS, joints, and lymph nodes	Ocular manifestations rare and occur late in disease course Usually accompanied by GI symptoms Uveitis, retinitis, retinal hemorrhages, choroiditis, keratitis, optic nerve edema, or optic nerve atrophy	Cytologic diagnosis: (PAS)–positive macrophages 16S ribosomal DNA gene amplification in vitreous specimens or cerebrospinal fluid (CSF) PCR of aqueous or vitreous	TMP-SMX most widely used Third-generation cephalosporins and rifampin also commonly used in conjunction	Variable, worse if optic nerve involved Disease can relapse once treatment stopped
Viruses							
Rift Valley fever	*Bunyaviridae*	Sub-Saharan and North Africa, Arabian Peninsula Virus primarily infects domesticated cattle Transmitted to humans by mosquito bite or contact with infected animals Occurs in epidemics	Incubation: 3–7 days Flu-like febrile illness lasting 2–4 days Other manifestations include hepatitis, thrombocytopenia, bleeding tendencies, rarely encephalitis Death infrequent but can have neurological sequelae	Up to 20% of patients Presents 4–15 days after systemic symptoms begin Most common ocular manifestation: macular retinitis Other ophthalmic lesions included retinal hemorrhages, vitritis, optic disk edema, and retinal vasculitis Anterior uveitis present in up to 1/3 of patients	Detection of outbreaks helpful Serum IGM and IGG testing CSF IGM testing in encephalitis Virus isolation by specialized virus labs PCR may be helpful	Supportive Prevention of exposure to halt outbreaks	Usually mild and self-limited Ocular involvement may cause permanent visual loss due to macular scarring or optic atrophy

Dengue fever	Dengue virus (*Flavivirus*)	Very common worldwide 100 million people annually Tropical and subtropical regions Transmitted by *Aedes aegypti* mosquito	Characterized by high fevers Other symptoms include headaches, myalgia, and bleeding manifestations (due to thrombocytopenia) Hypotension may occur in *dengue shock syndrome*, which carries high mortality rate	Ocular involvement in up to 10% of patients hospitalized Subconjunctival hemorrhage common Characteristic "dengue maculopathy" usually bilateral and involves both retina and choroid Dengue maculopathy presents 1 week after onset of fever Other posterior manifestations include retinal hemorrhage, retinal vascular sheathing, yellow subretinal dots, RPE mottling, macular edema, disk edema	Typical clinical presentation often diagnostic Dengue IGM can be measured Dengue maculopathy diagnosis based on clinical features and retinal imaging	Supportive Systemic corticosteroids and immunoglobulin infusion has used with varying success	Ocular involvement may cause permanent visual loss due to macular scarring or optic atrophy Amount of visual loss likely depends on amount of large retinal vessel involvement

(continued)

Table 6.2 (continued)

Disease	Causative organisms	Epidemiology	Common history and symptoms	Ocular manifestations	Diagnostic testing	Treatment	Prognosis
Chikungunya	Chikungunya virus (*Alphavirus*)	Originally endemic in parts of Africa More infectious strains spread from Kenya in 2004 to islands in Indian Ocean and then through Asia and parts of Europe In 2013, large outbreak spread through Americas Transmitted via several mosquito species, usually *Aedes aegypti*	Incubation: 2–5 days Usually self-limiting febrile illness lasting days to weeks Most patients recover without consequences Increased morbidity seen with more recent strains Other features include headache, fatigue, myalgia, diffuse maculopapular rash, bleeding from nose or gums, peripheral edema, joint pain, hepatitis, multi organ failure Main distinguishing clinical feature is prolonged fatigue, lethargy, and depression lasting weeks Severe polyarthralgia may persist for months or years	May be unilateral or bilateral May present acutely or after resolution of systemic manifestations Acute anterior uveitis and retinitis most common Anterior uveitis can mimic herpetic uveitis Chikungunya retinitis, often associated with retinal vasculitis, usually affects the posterior pole Other ocular manifestations include panuveitis, panophthalmitis, optic neuritis, keratitis, episcleritis, neuroretinitis, and central retinal artery occlusion	Complete blood counts early in disease may reveal leukopenia, lymphocytosis, thrombocytopenia Virus isolation and PCR may be used in acute phase (7 days), while IGM testing useful after 10 days	Supportive For ocular disease, local corticosteroids, topical antihypertensives Systemic corticosteroids may be used Systemic acyclovir or valacyclovir may be considered for severe retinitis, although no evidence to support efficacy	Infection thought to confer lifelong immunity Typically benign and self-limiting Ocular involvement may cause permanent visual loss due to macular scarring or optic atrophy

Coxsackievirus	Coxsackievirus (enterovirus)	Grouped as "type A" and "type B" serotypes Hand, foot, and mouth disease most well known (usually type A16) Usually brief and benign Most common in children	Systemic symptoms highly variable, usually nonspecific flu-like symptoms Group A viruses tend to cause skin and mucous membrane eruptions Group B viruses may cause respiratory and GI symptoms, meningoencephalitis, myocarditis, pericarditis, and myositis	Rare Coxsackievirus B3, B4, and hand-foot-mouth disease Retinitis or chorioretinitis may occur, usually deep retinal white lesions similar to other white dot syndromes Occlusive retinal vasculitis may be visualized Cases of unilateral acute idiopathic maculopathy reported	Serological antibody testing	Supportive Topical or periocular corticosteroids may be considered for intraocular inflammation	Findings resolve spontaneously, usually without severe visual sequelae

(continued)

Table 6.2 (continued)

Disease	Causative organisms	Epidemiology	Common history and symptoms	Ocular manifestations	Diagnostic testing	Treatment	Prognosis
Protozoa							
Malaria	*Plasmodium* species (*P. falciparum, P. vivax, P. malariae, P. ovale, P. knowlesi*)	Worldwide health problem resulting in death of over 1 million people annually Caused by infection of erythrocytes Protozoa transmitted by mosquito bite, most commonly *Anopheles* mosquito Endemic to parts of Africa, Asia, and Latin America (species vary regionally) Most US cases imported from endemic regions	High fevers and flu-like illness common Appears weeks to months after inoculation During incubation, organism goes through number of morphologic changes affecting liver and erythrocytes Severe malaria may manifest as coma (cerebral malaria), metabolic acidosis, severe anemia, hypoglycemia, acute renal failure, or acute pulmonary edema Severe complications often fatal	Retinal changes in severe malaria can be of pathophysiological, prognostic, and diagnostic significance Malaria retinopathy: retinal whitening (macular or peripheral), vascular discoloration (white or orange), retinal hemorrhages (particularly with white centers), and papilledema Retinal findings in up to 1/3 of patients with severe malaria	Should be suspected in patients with extremely high fevers and from or recently visited an endemic area Hematopathology may show malaria parasites Serum antigen testing	Systemic treatment for malaria complex if resistant strains Treatment of P. falciparum involves combination of artemisinin derivative with a longer-acting partner drug Chloroquine may be used for other species Supportive treatment with antipyretic medications (e.g., acetaminophen)	Malaria retinopathy indicator of risk of severe organ damage or death Retinal findings resolve over 4–8 weeks, usually with visual improvement Vision may continue to be poor with severe retinal vascular occlusion or optic neuropathy

Parasites							
Onchocerciasis "river blindness"	*Onchocerca volvulus*	Transmitted by *Simulium* blackfly, which lives and breeds in rivers Affects over 35 million people worldwide Most abundant in Africa, but also Mediterranean, Central and South America	Complex life cycle of organism: Female blackfly ingests microfilariae from human blood Microfilariae develop into larva in the fly, then transmitted to humans via blackfly bite Larvae develop into adult worms, which settle in subcutaneous tissue and form fibrous nodules Adult worms then give rise to microfilariae Microfilariae spread throughout the skin, often causing intense skin itching and depigmentation Death of microfilariae causes severe inflammation	Caused by migration of microfilariae to the eye and the subsequent inflammatory response caused by their death Can cause limbal edema, hyperemia, conjunctival nodules, punctate keratitis, sclerosing keratitis, uveitis Less commonly, chorioretinitis, geographic retinal atrophy, optic atrophy Blindness due to corneal vascularization, glaucoma, complicated cataract, chronic chorioretinitis, optic atrophy	Skin biopsy and demonstration of microfilaria (sensitivity low unless palpable skin nodule) The Mazzotti test: a skin patch of diethylcarbamazine (DEC) causes localized microfilarial death Antibody tests may aid in diagnosis	Ivermectin most commonly used, but does not eliminate adult worm Doxycycline can sterilize or kill adult worms as it targets endosymbiotic bacteria in the worm Moxidectin is a new drug, maybe better than ivermectin	Variable depending on location and severity
Gnathostomiasis	*Gnathostoma spinigerum* or *Gnathostoma hispidum* (nematode)	Tropical and subtropical regions Endemic in parts of Asia and Latin America Caused by exposure to raw meat	Classic triad of symptoms: recurrent migratory swellings, eosinophilia, and travel to endemic area Symptoms usually occur in evening because of increasing motility of the worms at that time	Ocular involvement includes visualization of the worm in the eye Secondary effects include lid swelling, iritis, iris atrophy, iris holes, intraocular hemorrhage, retinal scarring, retinal detachment, glaucoma	Definitive diagnosis depends on isolation of the worm	Surgical removal of the worm necessary	Variable depending on location and severity

(continued)

Table 6.2 (continued)

Disease	Causative organisms	Epidemiology	Common history and symptoms	Ocular manifestations	Diagnostic testing	Treatment	Prognosis
Cysticercosis	*Cysticercus cellulosae* (larval form of *Taenia solium* or *Taenia saginata*)	Caused by ingestion of undercooked meat (usually pork) Affects 50 million people worldwide Endemic areas include Mexico and Latin America, sub-Saharan Africa, India, and East Asia	Neurocysticercosis is most common manifestation and causes substantial human morbidity and mortality CNS involvement manifests as neurological defects, hydrocephalus, and meningitis	Ocular findings: inflammation and cyst formation at infection site Inflammation of eyelids, subconjunctival tissue, extraocular muscles, orbit, anterior chamber, vitreous, or subretinal space Translucent cyst with visible undulating movements gives the nickname "living pearl" Rupture of cyst causes severe intraocular inflammation	Neuroimaging required to rule out CNS involvement Histopathological testing is confirmatory	Oral albendazole and prednisolone Surgical removal of parasite	Variable depending on location and severity

GI gastrointestinal, *CNS* central nervous system, *IGM* immunoglobulin M, *IGG* immunoglobulin G, *PCR* polymerase chain reaction

Rarely, cytomegalovirus (CMV) or Epstein–Barr virus (EBV) may be the etiological agent. VZV and HSV-1 are more likely in older patients, while HSV-2 is more common in young adults and children [99]. In patients with concomitant encephalitis or meningitis, the most likely pathogenic agents are HSV-1 and HSV-2, respectively.

Presentation

ARN is characterized by multifocal patches of retinal necrosis with discrete borders, usually starting in the peripheral retina, rapid progression of disease, circumferential spread, occlusive retinal vasculitis affecting arterioles preferentially, and moderate to severe inflammation in the vitreous and anterior chamber [100]. ARN is usually unilateral but can be bilateral (10–30 %) [101, 102]. PORN is characterized by a similar appearance of multifocal necrotizing retinitis with relatively little vitreous inflammation. PORN often involves the posterior pole on presentation but can involve any portion of the retina [103]. PORN is more rapidly progressive than ARN, and bilateral involvement is more common (up to 80 %) [104, 105].

Patients with ARN may present with eye redness, achy pain, photophobia, and/or vision loss. Anterior segment examination may demonstrate conjunctival and episcleral inflammation and either granulomatous or non-granulomatous inflammation. Examination of the posterior segment may reveal vitreous inflammation, retinal arteriolar sheathing, multifocal necrotizing retinitis, and/or optic nerve head edema

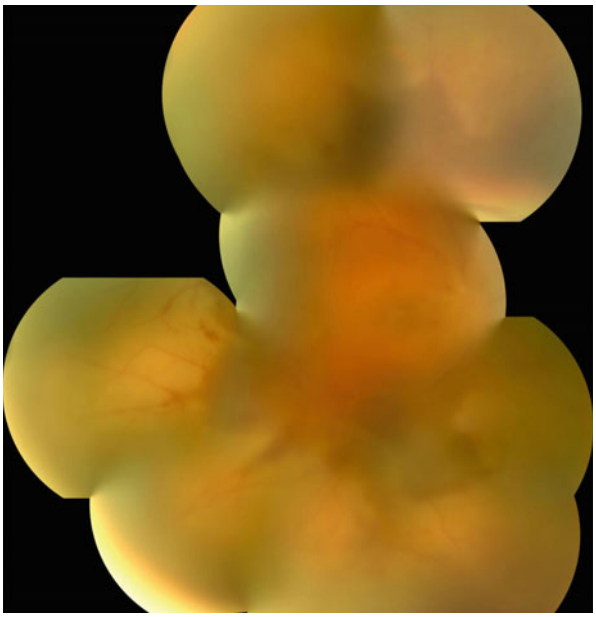

Fig. 6.12 Acute retinal necrosis. PCR was positive for herpes simplex type 1 in the right eye. There was severe vitritis, and retinal examination revealed extensive and confluent chalky retinitis and severe occlusive retinal vasculitis. The optic disk was moderately edematous, and there was a small lesion of retinitis in the papillomacular bundle

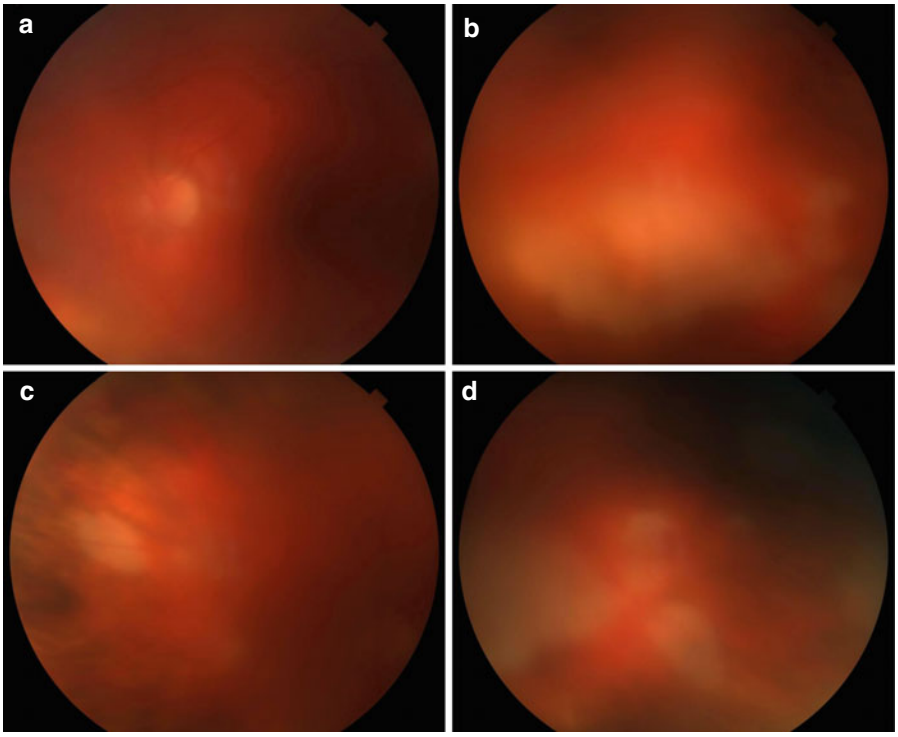

Fig. 6.13 Acute retinal necrosis. An anterior chamber paracentesis was positive for VZV. (**a**–**d**) Posterior examination revealed moderate vitritis and multifocal peripheral patchy retinitis lesions with discrete borders

(Figs. 6.12 and 6.13). Second eye involvement typically occurs within 6 weeks of presentation of the infection in the first eye but can occur months or years later [97].

As the active retinal infection resolves with treatment, affected areas develop pigmentary changes and retinal atrophy, often with a scalloped appearance at the junction of involved and uninvolved retina. Rhegmatogenous retinal detachment is a common consequence of infection and occurs in up to three-quarters of the eyes with ARN; retinal detachment may develop weeks to months after initial presentation of infection [106]. Other late complications of ARN may include chronic vitritis, macular edema, optic atrophy, epiretinal membrane formation, and recurrence of infection in the same or fellow eye [97].

Diagnostic Testing

Laboratory testing of intraocular samples is often valuable in the diagnosis of ARN and PORN. Past diagnostic techniques included antibody-based analysis of serum or intraocular fluid, viral culture, and pathological examination of retinal specimens [97]. More recently, PCR analysis of intraocular fluid has become the most commonly used test and may influence treatment in a portion of cases. A small sample of aqueous fluid is usually sufficient to detect VZV, HSV, or CMV DNA, and results

are typically available within 1 week. Specificity and sensitivity of these tests are high [107]. PCR testing for the herpes viruses is often done in conjunction with PCR testing for toxoplasmosis, which may mimic ARN in some cases [97].

Treatment

The mainstay of treatment in ARN and PORN is systemic antiviral medication, which can stop the progression of the disease and reduce the risk of bilateral involvement [102]. Historically, acyclovir has been the systemic drug of choice, and because the bioavailability of oral acyclovir is relatively low, patients treated with this agent typically undergo induction therapy with intravenous acyclovir, requiring hospitalization. The typical induction dose for acyclovir is 10 to 15 mg/kg divided three times a day for 7 days, followed by oral acyclovir 800 mg five times a day for 3–4 months [108]. With the advent of the newer oral agents valacyclovir and famciclovir, which have much greater bioavailability than oral acyclovir and can produce systemic concentrations nearly equal to those obtained with intravenous acyclovir, patients with ARN may be treated on an outpatient basis in some cases [109]. More specifically, oral agents may be considered in immunocompetent and compliant patients with relatively good vision. The initiating oral dose of valacyclovir is 1–2 g three times daily, and the initiating oral dose of famciclovir is 500 mg three times daily. Of note, these agents may cause renal toxicity; therefore renal function should be monitored.

Depending on treatment response and the type of virus involved, other systemic agents may be considered, including intravenous ganciclovir, intravenous foscarnet, and oral valganciclovir [97]. In cases of CMV, oral valganciclovir has good bioavailability and may be used similarly to valacyclovir for the other herpes viruses. The standard dose of valganciclovir is 900 mg twice daily for 3 weeks followed by 450 mg twice daily for maintenance. Although rare, some strains of HSV and VZV are resistant to acyclovir, and some strains of CMV are resistant to ganciclovir; most of these resistant cases respond to intravenous or intravitreal foscarnet [110]. Notably, ganciclovir may cause bone marrow suppression, and foscarnet may cause renal and central nervous system toxicity.

For certain severe cases, intravitreal injection of the antiviral medications foscarnet and/or ganciclovir may be considered for supplemental treatment of ARN or PORN, in conjunction with systemic antiviral therapy. Intravitreal foscarnet can be administered at a dose of 2.4 mg/0.1 ml, which requires no dilution from the commercially available intravenous solution. The typical dose of intravitreal ganciclovir is 2 mg/0.1 ml, which can be given two or three times weekly [97].

Prophylactic laser retinopexy to prevent retinal detachment has been advocated by some authors, although the recommendation for prophylactic laser as standard treatment has remained controversial [111]. In cases of retinal detachment, often there are both tractional and rhegmatogenous components, and vitrectomy is necessary to obtain anatomic reattachment of the retina. Some believe that early vitrectomy lowers the risk of retinal detachment, while others do not [97, 101].

In cases where significant inflammation is contributing to the vision loss, a course of oral corticosteroids may be considered. Corticosteroids should only be

used in conjunction with systemic antiviral medication. A loading dose of 0.5 mg/kg/day of prednisone for the first 7–10 days of treatment is typical [97]. The use of oral aspirin to prevent retinal vascular occlusion has been suggested as well, but its use has not been standard [112].

Prognosis

Prognosis in ARN is guarded, and poor prognostic indicators include immunosuppressed state, bilateral involvement, macular involvement, optic nerve involvement, and retinal detachment. In one series, 50 % of patients had 20/200 or worse visual acuity at 6 months follow-up [106].

Human Immunodeficiency Virus and Opportunistic Infections

Opportunistic infections manifest when the immune system is compromised for any reason. Immunodeficiencies may arise from a host of causes, including acquired immune deficiency syndrome (AIDS), malignancy, pharmacologic immunosuppression, uncontrolled diabetes mellitus, and other illnesses. Much of the study of opportunistic infections in the eye has occurred through research of patients with AIDS, but much of the discussion of opportunistic infections in this section may pertain to other causes of immunodeficiency.

AIDS is an expanding cause of morbidity and mortality worldwide, affecting over 30 million people [113]. It is caused by infection by the human immunodeficiency virus (HIV) retrovirus, which preferentially attacks CD4+ T-lymphocytes. The resultant immunodeficiency, termed AIDS, is caused by destruction of these cells and leads to the development of opportunistic infections, the main cause of illness and death in HIV-infected patients. HIV may be transmitted by sexual intercourse, blood-to-blood contact, transplacentally, or during breastfeeding.

Over 90 % of people with AIDS live in developing countries. Worldwide, the highest number of HIV-infected individuals is in sub-Saharan Africa, but the number of new cases is increasing rapidly in other areas of the world, including India and Southeast Asia. The demographics in the USA have shifted, although men who have sex with men remain the highest risk group. Racial and ethnic minorities represent a disproportionately high portion of those affected in the USA [114]. In the majority of cases in underdeveloped parts of the world, HIV transmission occurs through heterosexual contact [113].

The advent of highly active antiretroviral therapy (HAART) in the late 1990s has resulted in a marked reduction in mortality and a decreased incidence of associated opportunistic infections and neoplasms, including those of the eye. However, despite development of HAART, many patients in underdeveloped countries do not have access to these medications, and ocular manifestations of AIDS may affect 50–75 % of infected persons at some point in their disease course if left untreated with HAART. Ocular manifestations may be caused by extraocular (e.g., neuro-ophthalmic) and intraocular infection. Ocular manifestations caused by intraocular

infection will be discussed in this section and may be divided into three categories: HIV retinopathy, opportunistic malignancies, and opportunistic infections [115].

HIV Retinopathy

Retinal microvasculopathy, termed *HIV retinopathy*, is the most common ocular manifestation of HIV. It affects up to 60 % of HIV-positive patients at some point during their disease if untreated with HAART. The prevalence of retinal microvascular changes increases as CD4 counts decrease. Forty-five percent of HIV-positive patients with CD4 count less than 50 cells/μl will have clinically evident microvasculopathy, versus only 16 % who have CD4 counts greater than 50 cells/μl [116].

HIV retinopathy manifests as cotton-wool spots, usually in the posterior pole. Microaneurysms may also be apparent. Cotton-wool spots are usually small and can be distinguished from CMV retinitis by their typically smaller size, a lack of associated retinal hemorrhage, and lack of enlargement over time. Most patients with retinal microvasculopathy are asymptomatic, although larger cotton-wool spots in the posterior pole may cause small scotomata [117]. Rarely, macular edema due to microvascular disease may cause blurred central vision [118]. The pathophysiology of HIV retinopathy is unclear; histopathologic findings resemble those in diabetic retinopathy [119]. Treatment of HIV retinopathy is not typically indicated, but its presence is a marker of severe immunodeficiency [115].

Opportunistic Lymphoma

Non-Hodgkin B-cell lymphoma (NHL) is a malignancy associated with Epstein–Barr virus infection in patients with HIV/AIDS. Intraocular involvement may rarely occur and is usually associated with central nervous system and/or systemic involvement in the AIDS population [120]. Intraocular manifestations of NHL include vitritis, retinitis, retinal vasculitis and vascular occlusion, multifocal choroiditis, subretinal mass, and anterior uveitis. NHL should be considered in cases of retinitis unresponsive to antiviral and other antibiotic medications. If the diagnosis is unknown, a diagnostic vitrectomy may be performed; cytological examination of the vitreous will show neoplastic cells characteristic of large cell lymphoma [115]. Magnetic resonance imaging is warranted to determine presence of central nervous system involvement. Treatment options include radiation and chemotherapy. Prognosis for survival in AIDS patients with central nervous system lymphoma is poor [121].

Opportunistic Infections

A variety of systemic opportunistic infections associated with HIV/AIDS may cause intraocular infection. Because systemic treatment often cannot fully eradicate these infections, treatment typically begins with an “induction” phase and is then

continued in a "maintenance" phase. Maintenance treatment may sometimes be stopped once immunosuppression improves with induction of HAART therapy. Posterior segment opportunistic infections typically present as either necrotizing retinitis or multifocal choroiditis. When retinitis is associated with significant vitritis and anterior chamber inflammation, there is usually a higher CD4 count, and ARN, toxoplasmosis, syphilis, or cryptococcosis may be considered. If there is little intraocular inflammation, there is usually a lower CD4 count, and CMV retinitis and PORN are higher on the differential. Toxoplasmosis, cryptococcosis, tuberculosis, and syphilis may present as retinitis or choroiditis, while *Pneumocystis* infection presents as choroiditis [115]. Discussion of many of these intraocular infections is discussed elsewhere in this chapter, but *Pneumocystis* infection, cryptococcosis, and CMV retinitis will be discussed here.

Pneumocystis

Pneumocystis carinii pneumonia was once one of the most common systemic opportunistic infections in AIDS patients in the industrialized world but is much less common in the era of HAART. Extrapulmonary infection is uncommon in patients with AIDS, but ocular involvement may occur. Ocular manifestations of *P. carinii* include conjunctivitis, orbital mass, optic neuropathy, and choroiditis. Choroidal infection is the most common ocular manifestation and is typically bilateral and multifocal; lesions are yellow and well-demarcated, usually located in the posterior pole, and are not associated with intraocular inflammation or retinal vasculitis [122]. Prior to HAART, pneumocystis choroiditis was an indication of disseminated infection in severely immunocompromised patients, and median survival following diagnosis was less than 1 year [123]. Ocular lesions respond in most cases to induction and subsequent maintenance treatment with systemic pentamidine, trimethoprim and sulfamethoxazole, or dapsone [123].

Cryptococcus

Cryptococcus in HIV/AIDS typically causes meningitis; therefore the most common ocular manifestations are neuro-ophthalmic. Cryptococcal choroiditis is the most common intraocular manifestation, and the source may be hematogenous spread from the lungs or direct extension from cryptococcal meningitis. Choroidal lesions may be multifocal, solitary, or confluent (Fig. 6.14) [124]. Other ophthalmic manifestations include eyelid nodules, conjunctival mass, granulomatous iritis, iris mass, vitritis, necrotizing retinitis, endophthalmitis, and optic neuritis [115]. Treatment of cryptococcal choroiditis is systemic intravenous antifungal medication; therapy should be determined by an infectious disease specialist. Although infection may respond to therapy, visual outcome is often limited by optic atrophy, which may be due to the infection itself or secondary to high intracranial pressure and resulting optic nerve damage [115].

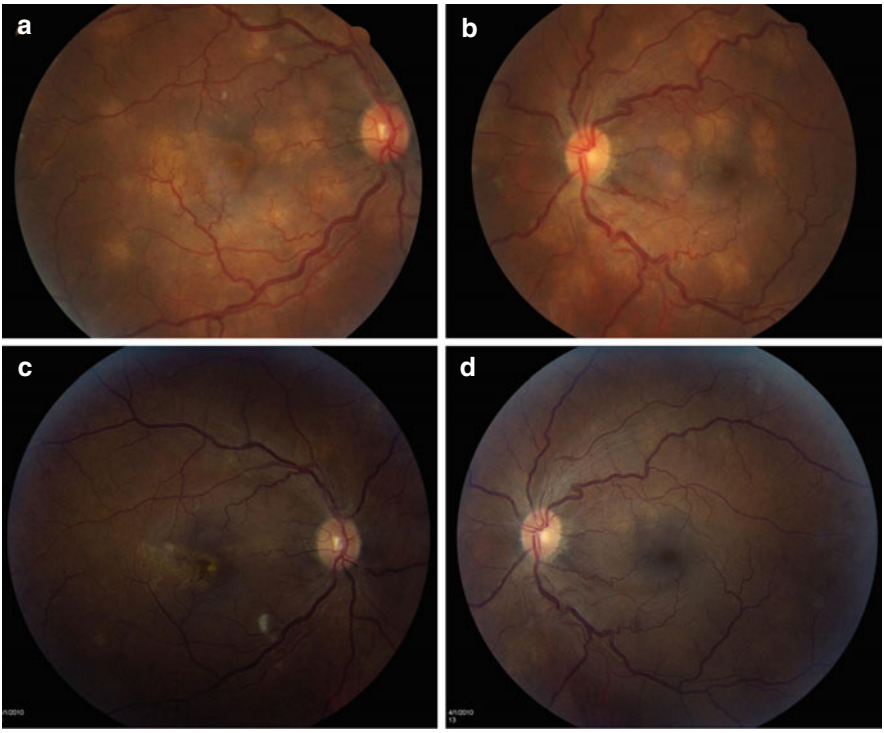

Fig. 6.14 Cryptococcus chorioretinitis. *Cryptococcus* antigen in the spinal fluid was highly positive (1:256). Blood cultures were eventually positive for *Cryptococcus*. The patient was HIV-positive with poor follow-up. (**a**, **b**) Fundus examination revealed no intraocular inflammation and multiple choroidal yellow plaque-like lesions, involving the macula in the right eye and sparing the macula in the left eye. (**c**, **d**) Visual acuity and fundus findings improved with antifungal treatment

Cytomegalovirus Retinitis

CMV retinitis was extremely common in the USA in the era before HAART therapy; around one-third of patients with AIDS in the USA would develop CMV retinitis [125]. CMV retinitis occurs only in severely immunodeficient patients, nearly always with CD4 counts of less than 50 cells/μl. In the era preceding HAART, therefore, life expectancies of patients who presented with CMV retinitis were extremely low, usually less than 1–2 years. In underdeveloped countries, the relatively low incidence of CMV retinitis is likely due to low life expectancy, i.e., patients die before developing CMV retinitis [113].

The clinical appearance of CMV retinitis is usually distinctive. Infection usually starts as a solitary lesion, in contrast to the retinitis in ARN and PORN. Advancement of infection into normal retina is characterized by a dry granular border with multiple dot-like satellite lesions. Other than the retinitis, intraocular inflammation is typically minimal. Spread of the infection is relentless without treatment with anti-

viral medication and HAART [113]. Patients may present with either a more fulminant form, characterized by retinal necrosis with hemorrhage that develops in the posterior retina, or a more indolent form, seen as a granular lesion in the peripheral retina, often with little or no associated hemorrhage. An uncommon presentation is frosted branch angiitis [115]. Because a sizeable minority of patients with CMV retinopathy are asymptomatic, routine ophthalmoscopic screening has been recommended at 3-month intervals in severely immunocompromised individuals with CD4 counts less than 50 cells/ul [126].

For treatment of CMV retinitis in AIDS patients, intravenous ganciclovir, foscarnet, or cidofovir may be used. More recently, oral valganciclovir, a prodrug of ganciclovir with excellent bioavailability, has been used to treat CMV. Notably, all of these drugs only inactivate and do not eradicate the infection; therefore they must be continued until the patient is no longer severely immunocompromised. In many cases, signs of disease activity persist despite treatment with these drugs, especially late in the course of disease; therefore additional initiation with HAART is critical to eradicate the disease [113].

In combination with systemic therapy, local intravitreal injections of either ganciclovir or foscarnet may be used to achieve high drug levels (as discussed in the Sect. 6.1). To achieve adequate dosage, injections must be given 2–3 times weekly; for this reason, the ganciclovir implant was developed, which released relatively high intraocular drug levels for approximately 8 months [113]. However, because of the rapid decline in incidence of CMV retinitis with the advent of HAART, the ganciclovir implant is no longer in production, and its use is now historical.

Besides systemic treatment with anti-CMV medication, the most important treatment of newly diagnosed CMV retinitis is to start HAART in patients who have not yet started HIV treatment or to reestablish immune recovery by switching medications in patients who are already receiving HAART medication. In some practices, HAART therapy initiation may be delayed until treatment for CMV is started to reduce the risk of systemic inflammatory reactions against the pathogens released during immune recovery [113]. Once immune recovery has been achieved, meaning sustained CD4 counts of greater than 100 cells/uL for 6 months, treatment for CMV may be stopped as long as there are no signs of persistent infection [127]. CMV retinitis can reactivate after anti-CMV drugs are stopped; therefore patients must be monitored for recurrence. The most helpful laboratory indicators are CD4 count and HIV viral load [128].

Immune recovery uveitis is a complication of treatment of CMV retinitis patients with HAART; it is caused by immune reaction to CMV antigens made worse by recovery of the immune system with treatment of HIV/AIDS [129]. The most severe inflammatory response usually begins within several weeks after starting HAART, and complications include macular edema, epiretinal membrane, retinal neovascularization, and a host of other complications of severe uveitis. Patients with immune recovery uveitis may require local or systemic corticosteroids to treat inflammation; systemic CMV infection is usually eradicated once immune recovery is achieved, and systemic anti-CMV medications may often be stopped [113].

Although not as common as in ARN, retinal detachment is a common complication of CMV retinitis. In the era before HAART, retinal detachments occurred in

more than one-third of patients with CMV retinitis who survived 1 year or longer. More recently, the risk of detachment is substantially less among patients receiving HAART, perhaps because of better infection control resulting in smaller lesions and more adherent scars [130]. As in ARN, retinal detachment is often due to a combination of tractional and rhegmatogenous components, and treatment requires vitrectomy with laser and either gas, or more commonly, silicone oil tamponade.

West Nile Virus

West Nile virus (WNV) infection is caused by an enveloped single-stranded RNA *Flavivirus*, passed to humans by the *Culex* mosquito, with wild birds serving as the reservoir. Much more rarely, blood-to-blood or transplacental transmission may occur [131]. It is present in many parts of the world including Africa, Europe, Australia, and Asia, and, since 1999, it has spread rapidly throughout many parts of the Western hemisphere, including the USA [132]. Peak season for contraction of the disease is in the summer months.

Presentation
Incubation lasts between 2 and 14 days. About 80 % of human infections are asymptomatic; only 20 % of people develop symptoms. Symptomatic patients usually have a self-limited febrile flu-like illness, which usually lasts less than a week. Fever is often high grade (>39 °C). Severe neurologic disease (meningoencephalitis) is rare, occurring in approximately 1 % of patients, and is associated with advanced age and diabetes mellitus [131]. Patients with WNV meningoencephalitis may present with a wide variety of neurological symptoms following more typical systemic complaints earlier in the disease.

Several ophthalmologic findings have been recognized, including chorioretinitis, anterior uveitis, retinal vasculitis, and optic neuritis. Multifocal chorioretinitis is the most common finding, occurring in almost 80 % of patients with acute WNV infection and associated neurologic illness [133]. An associated mild to moderate vitritis is frequently observed. Most patients have minimal or no ocular symptoms. Active chorioretinal lesions appear as small circular deep creamy lesions, while inactive chorioretinal lesions are atrophic and partially pigmented with a “target-like” appearance. Chorioretinal lesions nearly always involve the periphery but also often involve the posterior pole. Linear clustering of chorioretinal lesions is common, sometimes mirroring the course of retinal nerve fibers [134]. Other ophthalmic manifestations include anterior uveitis, vitritis, retinal hemorrhages, optic nerve edema, and retinal vascular sheathing.

Diagnostic Testing
Serum testing may be helpful in diagnosis of infection with WNV. The most common serum test is detection of WNV IgM antibodies in serum with an enzyme-linked immunosorbent assay (ELISA). Testing for IgM antibodies may also be

performed on cerebrospinal fluid to confirm infection of the central nervous system; positive testing confirms WNV meningoencephalitis [131, 135]. Cross-reactivity may occur with other similar viruses, and special testing may be necessary to differentiate WNV from infection with one of these other viruses [131].

Treatment
There is, at present, no proven treatment for WNV infection, but supportive therapy is indicated in severe cases. Prevention of mosquito bites is the mainstay in reducing possibility of infection. Topical corticosteroids may be helpful for cases of anterior uveitis, and various ophthalmic treatments may be indicated for secondary ophthalmic complications (e.g., panretinal photocoagulation for retinal neovascularization) [90].

Prognosis
The outcome of WNV systemic disease is good in most patients, but neurologic sequelae or even death may occur in severe cases of WNV meningoencephalitis [135]. Ocular manifestations are usually self-limited. Inactive choroidal lesions may leave behind pigmented scars and can sometimes cause visual impairment if involving the macula or optic nerve. Rarely, severe occlusive retinal vasculitis may result in retinal neovascularization and its sequelae [90].

Rift Valley Fever

Rift Valley fever (RVF) is an arthropod-borne viral zoonosis caused by Bunyaviridae. The virus primarily infects domesticated cattle. It is transmitted to humans by either mosquito bite or through contact with infected animals, and the disease can occur in epidemics. RVF has been found in sub-Saharan and North Africa and more recently in the Arabian Peninsula [90, 136–138]. For additional information, see Table 6.2.

Dengue Fever

Dengue fever is the most common mosquito-borne viral zoonosis in humans. It is caused by the dengue virus, a *Flavivirus*, and is transmitted by the *Aedes aegypti* mosquito. It is common in tropical and subtropical regions and afflicts 100 million people annually [139]. See Table 6.2 for additional information.

Chikungunya

Chikungunya virus is an arthropod-borne *Alphavirus* that causes epidemics of human disease by transmission via several mosquito species, usually *Aedes aegypti*. It was originally endemic in parts of west, central, and southern Africa. In 2004,

novel and highly contagious strains emerged in Kenya, which then spread to several islands in the Indian Ocean, most notably La Reunion. These more infectious strains continued to spread throughout Asia, and subsequently a few outbreaks were seen in Europe. In 2013, a large outbreak began to spread through the Americas, and the virus has now been noted in the Caribbean, Central America, South America, and Mexico [90, 138, 140–146]. See Table 6.2 for additional information.

Coxsackievirus

Coxsackievirus is a type of enterovirus that may cause a variety of syndromes in humans. A number of different serotypes are known, grouped into "type A" and "type B," some of which have been reported to rarely cause ocular symptoms in addition to systemic disease. The most well-known syndrome related to the virus is hand, foot, and mouth disease, which is frequently associated with Coxsackievirus type A16 [147–151]. The disease is usually brief and benign and most common in children. For additional information, see Table 6.2.

Protozoa and Parasites

Ocular Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan parasite and is the most common cause of infectious posterior uveitis in the world. It is most prevalent in South and Latin America as well as Africa and parts of Asia, where seropositivity may be over 80%, but the organism is found in many other parts of the world, including the USA (seropositivity around 10%) [152].

T. gondii exists in three states: oocysts, tachyzoites, and bradyzoites. Oocysts are the product of the parasite's sexual cycle in the intestine of felines and release infectious sporozoites in cat feces. Tachyzoites are asexual forms that arise after ingestion of sporozoites by the new host that damage host tissue through rapid replication. Tachyzoites transform into bradyzoites after the host immune system begins attacking the parasite. Bradyzoites are cysts that reside dormant in tissues and replicate slowly without causing significant disease unless they reactivate into the tachyzoite state again. In humans, bradyzoites are often harbored in the central nervous system, including the eye.

Humans become infected by ingestion of undercooked cyst-contaminated meat products or by sporulated oocysts from cat feces, which can be found in contaminated water, soil, or on vegetables [153]. Toxoplasmosis is a well-known cause of congenital infection; however, most cases are contracted after birth [154].

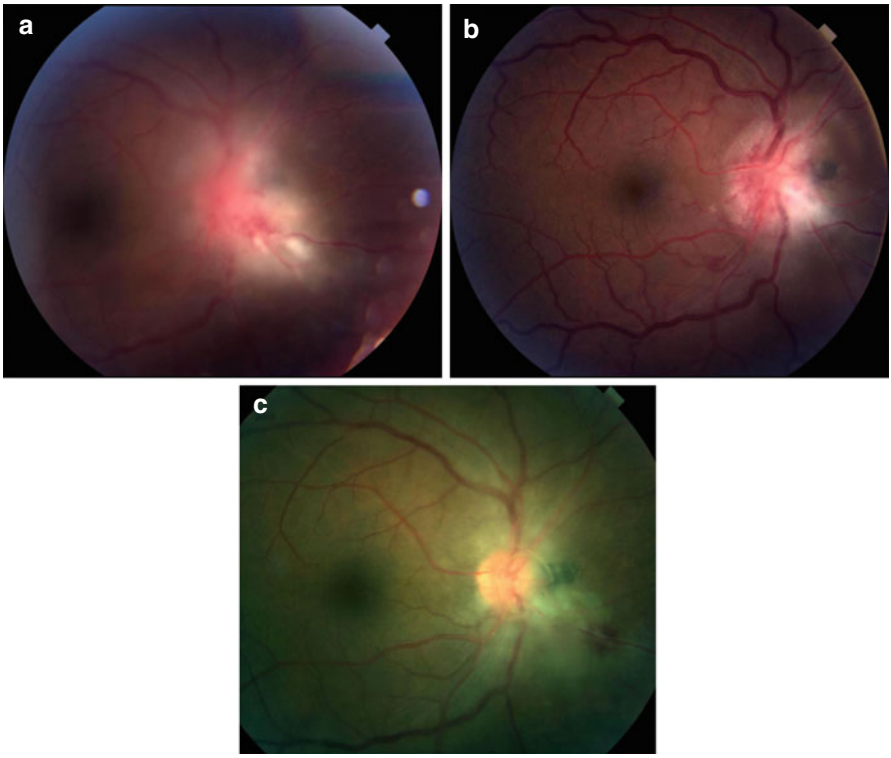

Fig. 6.15 Ocular toxoplasmosis. An anterior chamber paracentesis was negative for toxoplasmosis via PCR. Serum testing was positive for toxoplasmosis IgG. (**a**) Moderate vitritis and severe optic nerve inflammation, with fluffy white chorioretinal infiltrates evident on the nasal border of the optic disk, and sheathing of the peripapillary retinal vessels. (**b**) Over 2 weeks, inflammation improved with trimethoprim/sulfamethoxazole. (**c**) By 2 months, a peripapillary chorioretinal scar became evident, suggesting secondary retinitis and papillitis secondary to prior ocular toxoplasmosis

Presentation

Necrotizing focal chorioretinitis with overlying vitritis, the classic "headlight in fog" if vitritis is dense, is the typical ocular presentation of toxoplasmosis, but a variety of other presentations may be manifest. However, intraocular inflammation does not occur in the absence of a retinal lesion. In secondary infection, the infection is reactivated at the site of a preexisting chorioretinal scar, and retinitis appears adjacent to the scar; 70 % of cases that present to ophthalmologists are due to secondary infection (Fig. 6.15) [155]. In primary infection, no chorioretinal scar has yet developed. The retinitis in toxoplasmosis may be difficult to distinguish from ARN secondary to viral infection, and testing and treatment for both conditions may be warranted initially (Fig. 6.16). Congenital toxoplasmosis may be difficult to distinguish from acquired toxoplasmosis, but congenital lesions are more commonly found in the macula and are more likely to be bilateral [155].

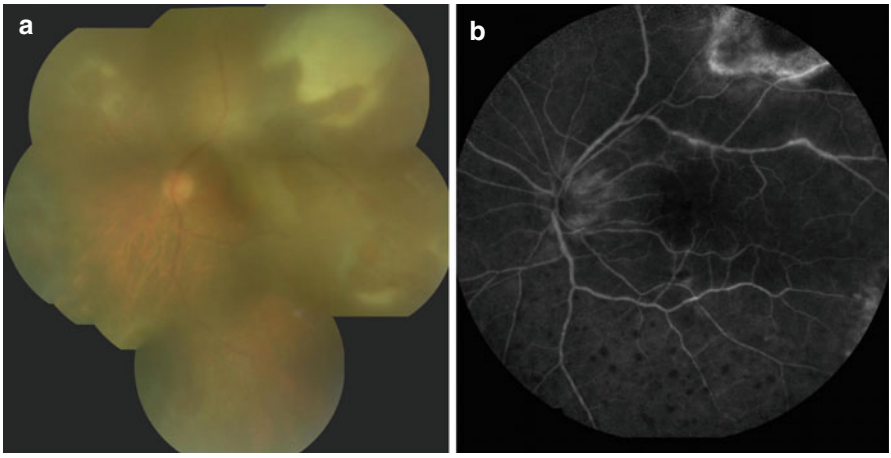

Fig. 6.16 Retinitis secondary to toxoplasmosis. Vitreous paracentesis was positive for toxoplasmosis via PCR. (**a**) Moderate vitritis is evident. There is diffuse preretinal fibrosis over the posterior pole. There are multifocal patches of discrete retinitis, most notably superotemporally. No chorioretinal scar suggestive of toxoplasmosis is evident. (**b**) Fluorescein angiography demonstrates staining of the retinal veins and early hyperfluorescence with late leakage at the border of retinitis superotemporally. The optic nerve is hyperfluorescent

An unusual but well-described presentation of primary or secondary intraocular toxoplasmosis is punctate outer retinal toxoplasmosis (PORT), characterized by multifocal small lesions in the deep retina and RPE. Because the inflammation is focal and deep, there is usually minimal associated vitritis. After resolution of PORT, granular white lesions may remain, and often patients are left with visual loss due to optic neuropathy [156]. Patients with PORT are usually in the pediatric age group and may arise from either congenital or acquired infection [153].

Other presentations may include neuroretinitis with a macular scar, scleritis, granulomatous anterior uveitis, trabeculitis, retinal vasculitis, proliferative vitreoretinopathy, and vitreous hemorrhage and tractional retinal detachment due to secondary retinal neovascularization [153]. Retinal arteriolar plaques, or Kyrieleis plaques, may occur adjacent to the active toxoplasmosis retinitis but are not characteristic of toxoplasmosis.

Patients who present with secondary infection are usually young adults between the ages of 20 and 40 years, while those that present with primary toxoplasmosis infections are usually older, between 40 and 60 years [155]. Recurrence is common, occurring in up to 80 % of patients followed for at least 5 years [155, 157]. Severe presentations of ocular toxoplasmosis may be associated with older age or immunocompromised states, including HIV/AIDS [153].

Diagnostic Testing

Serum testing, usually ELISA, may be helpful in distinguishing primary toxoplasmosis, in which IgM or IgA antibodies may be present, from cases of reactivation. Presence of IgG antibodies is a sign of prior infection; a positive

toxoplasma IgG may be of little diagnostic benefit in populations with high seropositivity rates [158].

Testing of intraocular specimens, whether aqueous or vitreous humor, may be helpful in diagnosis of ocular toxoplasmosis. Both PCR testing and detection of intraocular toxoplasma-specific antibodies may be utilized. Intraocular antibody synthesis is determined by the Goldmann–Witmer coefficient (GWC), which is based on the comparison of the *T. gondii*-specific antibodies in the aqueous humor and in the serum in relation to the globulin titers in the same fluids. A high coefficient indicates active toxoplasmosis infection [159]. However, the time interval before activation of local antibody production may vary, and false negatives may occur when using the GWC alone; therefore more recently DNA amplification using PCR has become the test of choice when examining intraocular fluid specimens, either alone or in combination with antibody testing [153].

Treatment

Treatment of toxoplasmosis remains controversial, as there is disagreement regarding indications for treatment as well as ideal treatment regimen. In most immunocompetent patients with ocular toxoplasmosis, the intraocular inflammation is self-limited; therefore treatment may not be indicated if the active lesion is small and peripheral. Common indications for treatment include active retinitis with posterior lesions near the optic nerve or macula, large lesions >2 disk diameters, or lesions in immunocompromised individuals.

Antibiotic therapy is usually given for a 6–8-week course. Classic antibiotic therapy consists of three-drug combination therapy including pyrimethamine, sulfadiazine, and folinic acid. More recently, less toxic medications have become popular in the treatment of toxoplasmosis, including clindamycin, azithromycin, atovaquone, and trimethoprim/sulfamethoxazole. These medications have been used in combination or alone to treat ocular toxoplasmosis. However, there have been no definitive clinical trials examining the efficacy of these medications in improving visual outcomes or in decreasing rates of recurrence [160]. Alternatively, clindamycin (450 ug/0.1 ml) may be injected directly intravitreally, which provides more targeted antibiotic treatment for severe cases [161].

Corticosteroid therapy, either oral, periocular, or topical, may be administered in conjunction with antibiotic therapy in cases of severe vitritis or anterior chamber reaction. It is not recommended unless antibiotic therapy is given in conjunction, as the resultant immunosuppression caused by these medications may lead to fulminant and progressive infection [162].

Prognosis

Most cases of ocular toxoplasmosis are self-limited. Inflammation usually improves between 2 and 4 months after presentation. However, the macula and optic nerve may be involved, particularly in cases of congenital toxoplasmosis. Approximately 25 % of ocular toxoplasmosis cases may result in visual acuity of 20/200 or worse. In addition, recurrences are common; nearly 80 % of patients who were followed for more than 5 years had an episode of recurrence in one study [155].

Malaria

Malaria is a worldwide health problem, resulting in death of over 1 million people annually. It is caused by infection of erythrocytes by *Plasmodium*, which are protozoa transmitted to humans by mosquito bite, most commonly the *Anopheles* mosquito. There are five species of *Plasmodium*, the prevalence of which varies regionally: P. *falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. The disease is endemic to parts of Africa, Asia, and Latin America. New cases have been reported in the USA, although most cases in the USA are imported after travel to more endemic regions of the world [145, 163–166]. See Table 6.2 for additional information.

Toxocariasis

Toxocariasis is an infection caused by larvae of *Toxocara canis* (dog roundworm) and less frequently by *Toxocara cati* (cat roundworm). It is contracted by ingestion of soil or food products contaminated with embryonated eggs. Once ingested, larvae hatch in the small intestine and then migrate to tissues, most notably the lungs, muscle, and eyes. Larvae resident in human tissue never develop into adult organisms capable of reproduction [167]. The organism is common in many parts of the world, including the USA, but symptomatic *Toxocara* infection is comparatively rare [167].

Presentation
The systemic form of toxocariasis is termed "viscera larva migrans," which is characterized by fever, malaise, hepatosplenomegaly, rash, and leukocytosis. Ocular toxocariasis, or "ocular larva migrans," is the most common localized manifestation of *Toxocara*. Ocular toxocariasis lesions are unilateral 90% of the time and appear as a whitish mass involving the retina and peripheral vitreous. A fibrovascular band often runs between the lesion and the posterior pole or optic nerve (Fig. 6.17). The lesions may be associated with vitritis or vitreous haze early in the infection. Other manifestations include panuveitis, posterior pole granuloma, optic nerve granuloma, and vitreous lesions. It is one of the conditions that may cause leukocoria in the pediatric population [168].

Diagnostic Testing
Serologic testing is often inconclusive in ocular toxocariasis, and diagnosis may be difficult. Although eosinophilia is often present in systemic infection, this is often not the case in ocular toxocariasis. ELISA and calculation of Goldmann–Witmer coefficients may be performed on intraocular fluids to aid in diagnosis; PCR may be negative as *Toxocara* DNA is not often shed into intraocular fluids [167]. Vitreous biopsy and cytology may be helpful in difficult cases [169].

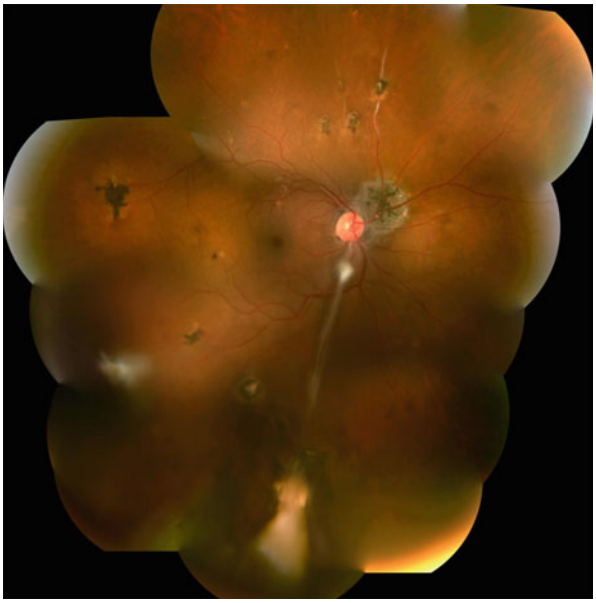

Fig. 6.17 Ocular toxocariasis. Fundus examination revealed findings suggestive of ocular toxocariasis: a whitish mass involving the retina and peripheral vitreous inferiorly, with a fibrovascular band running between the peripheral lesion and the optic nerve. There were a number of multifocal chorioretinal scars but no active inflammation

Treatment

Corticosteroids are the mainstay in treatment of intraocular inflammation and can be administered topically, periocularly, or systemically. Treatment with oral albendazole in ocular toxocariasis is controversial, as it is thought to increase inflammatory response in some cases as organism antigens are released [170]. There have been several reports of pars plana vitrectomy for ocular toxocariasis, which is indicated in cases of tractional or rhegmatogenous retinal detachment, endophthalmitis, or vitreous hemorrhage secondary to retinal neovascularization [167].

Prognosis

Visual prognosis in ocular toxocariasis is often poor and is often due to retinal scarring, detachment, or other sequelae from long-standing intraocular inflammation. In one report, one-third of patients had visual acuity of 20/200 or worse [171].

Diffuse Unilateral Subacute Neuroretinitis

The term *diffuse unilateral subacute neuroretinitis* (DUSN) was first used by Gass and Scelfo in 1978 [177]. They described a syndrome which included insidious severe loss of peripheral and central vision with associated findings of vitreous

inflammation, diffuse RPE changes with relative sparing of the macula, narrowing of the retinal vessels, optic atrophy, increased retinal circulation time, and subnormal electroretinographic findings. Dr. Gass then observed a nematode in two patients with similar presentation, and it became clear that the condition was due to migration of a nematode in the subretinal space [178].

Although nematodes are the causative organisms of DUSN, the exact etiological agent is often not clear. Parasites of different sizes and several species of nematodes have been reported as the possible etiologic agent of DUSN, including *Toxocara canis*, *Baylisascaris procyonis*, and *Ancylostoma caninum*, but most reports do not present conclusive evidence about the specific agent. The type of nematode likely varies depending on geographic region, as the average size of observed nematodes varies depending on region [179].

Presentation

The disease often presents in children or young adults. In the early stage, patients may present with scotomas or decreased visual acuity. Ocular findings include mild to moderate vitritis, mild optic disk edema, and multifocal evanescent whitish-yellow deep retinal and choroidal lesions [180]. The patchy choroidal lesions resolve spontaneously but may reappear along with migration of the worm. In the later stage, which is the more common presentation, diffuse degeneration and depigmentation of the RPE, usually most prominent in the peripapillary and peripheral retina, occur along with progressive optic nerve atrophy and arteriolar narrowing [181]. An intraocular worm may be seen in 25–40 % of cases and appears as a motile, white, glistening nematode that varies in length from 400 to 2,000 μm. The worms may sometimes leave tract-like RPE changes in the wake of movement [182].

Diagnostic Testing

Serologic testing, stool samples, and blood smears are often not helpful in DUSN. Eosinophilia may be seen in some cases and can aid in diagnosis. In both the early and late stages, electroretinograms are often diminished but not extinguished and can be helpful in making the diagnosis [179].

Treatment

If a worm is seen, it can be treated with laser photocoagulation without causing significant intraocular inflammation. In a series of 70 patients diagnosed with DUSN, Garcia and colleagues found a live worm in 4 patients in the early stage and in 22 in the late stage. After photocoagulation treatment, all the patients in the early stage but none in the late stage had improved visual acuity [180, 181]. Oral antihelminthic medications, most notable albendazole, may also be used, but the medications do not always kill the subretinal nematode [183, 184].

Prognosis

If caught early and treated, visual acuity often is minimally affected. Visual prognosis in late stages is poor, with 80 % of cases resulting in visual acuity of 20/200 or worse [181].

Onchocerciasis

Onchocerciasis, or "river blindness," is caused by infection of *Onchocerca volvulus*, which is transmitted by the *Simulium* blackfly, a species that lives and breeds in rivers and streams. The disease affects over 35 million people worldwide and is most abundant in Africa, but it may also be found in the Mediterranean and Central and South America [95, 172–176]. The life cycle of *Onchocerca volvulus* begins when the female blackfly ingests microfilariae from infected human blood. The microfilariae develop into larvae in the blackfly and are then transmitted to humans via blackfly bite. The larvae then develop into adult worms, which often settle in subcutaneous tissue and form fibrous nodules called onchocercomas. The adult worms within these nodules then give rise to microfilariae, which spread throughout the skin, often causing intense skin itching and depigmentation. Death of microfilariae often causes a severe inflammatory response [172–176]. See Table 6.2 for additional information.

Gnathostomiasis

Gnathostomiasis is caused by infection by the nematode *Gnathostoma spinigerum* or *Gnathostoma hispidum*. The disease is found in tropical and subtropical regions and is endemic in parts of Asia and Latin America. Humans become accidental hosts by ingesting undercooked or raw meat or through penetration of the skin during preparation of food [174, 185]. See Table 6.2.

Cysticercosis

Cysticercosis is caused by ingestion of undercooked meat (usually pork) containing *Cysticercus cellulosae*, the larval form of *Taenia solium* or *Taenia saginata*. It affects an estimated 50 million people worldwide. Endemic areas include Mexico and Latin America, sub-Saharan Africa, India, and East Asia [174, 186–188]. See Table 6.2.

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