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# Endogenous Endophthalmitis: Etiology and Treatment

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## Abstract

This chapter comprehensively covers all aspects of endogenous endophthalmitis from systemic infectious agents, with an emphasis on reported and newer etiologies to broaden the diagnostic and investigative acumen of treating ophthalmic providers. The discussion includes the etiology of metastatic endophthalmitis and diagnostic investigations, including polymerase chain reaction (PCR), for identification of bacterial and viral infections involving the eye in both immunosuppressed and non-immunosuppressed patients. Additionally, we present clinical and diagnostic findings of fungal infections, protozoal infections, and helminthic infections. Pediatric cases are also reported and etiologies described. We discuss both etiology and diagnostic challenges. Current therapeutic modalities and outcomes are reviewed. While no two cases of metastatic endophthalmitis are the same, some similarities may exist that allow us to generalize how to approach and treat this potentially sight- and life-threatening spectrum of diseases and find the underlying systemic cause.

**Keywords:** endophthalmitis, endogenous, bacterial, viral, fungal, protozoal, helminthic

## 1. Introduction endogenous endophthalmitis: etiology and treatment

Endophthalmitis is defined as any infectious inflammation of vitreous, retina, or choroid that may or may not involve the anterior chamber. A useful classification is to define the infectious agent as exogenous or endogenous depending on the route of infection. Exogenous endophthalmitis occurs from direct entry of pathogen(s) after disruption of ocular tissues, whether from trauma (like an open globe injury) or from surgical interventions (such as cataract or glaucoma surgery, intravitreal injection, or retinal surgery). Alternatively, endogenous endophthalmitis occurs when pathogens spread from other parts of the body to the eye (mainly by hematogenous spread but can also be neuronal in case of some viruses) with a subsequent compromise to the blood-ocular barrier. Since the choroid and the retina are highly vascularized, these structures may be seeded early in the systemic infection. In this chapter, we discuss endogenous endophthalmitis including the incidence, causes, and management of bacterial, viral, fungal, and other less common infectious agents.

## 2. Endogenous bacterial endophthalmitis (EBE)

While endogenous bacterial endophthalmitis comprises the minority (2–8%) of endophthalmitis cases, it is a devastating intraocular infection that often results in

poor visual outcomes, loss of the eye, and even mortality [1–4]. Nineteen percent of cases have a bilateral presentation [5]. Prompt recognition and treatment is vital for improved visual outcome. Unfortunately, many patients with EBE are either initially misdiagnosed (up to 25% of cases) or have a delay in diagnosis (a median of seven days) [2–4]. EBE is most commonly misdiagnosed as non-infectious uveitis but can also be mistaken for acute angle closure glaucoma, conjunctivitis, or orbital cellulitis [3, 4]. In children, EBE is most often misdiagnosed as retinoblastoma [3, 4].

Familiarity with common clinical features is crucial for proper diagnosis of EBE. Blurred vision (89%) and pain (48%) are common presentations, although they are not always present [3]. The most common systemic findings include fever (37%), often a low-grade fever and chills, and influenza-like features (20%) [3].

The absence of a clear view of the fundus is the most common ocular sign (40%), but other important exam findings include anterior chamber reaction (32%), hypopyon (35%), and vitritis (33%). Hypopyon color can be associated with different causative organisms. For example, *Staphylococcus aureus*, *Serratia marcescens*, and *Klebsiella* endophthalmitis can be associated with pink or blood-tinged hypopyon, whereas *Mycobacterium tuberculosis*, *Streptococcus bovis*, and *Listeria monocytogenes* endophthalmitis can present with tan or pigmented hypopyon [6]. Moreover, organisms such as *Listeria monocytogenes* and *Bacillus cereus* are commonly associated with elevated intraocular pressures [7].

Endogenous bacterial endophthalmitis is also known as metastatic endophthalmitis, since an extraocular (systemic) focus of infection is typically the source. Liver abscesses are the most common sources of infection followed by lung and cardiac infections [3]. Other foci include soft tissue infection, meningitis, urinary tract infection (UTI), brain, and renal abscesses. Moreover, patients diagnosed with EBE often have underlying medical conditions that lead to an immunosuppressed state such as Diabetes mellitus (DM), Human Immunodeficiency Virus (HIV) infection, autoimmune disease, and malignancy [3, 4]. Other predisposing factors for EBE include high-risk behaviors such as IV drug use (IVDU) and alcohol abuse [3].

These infections are often life-threatening, so investigations into underlying foci and risk factors are paramount. In fact, mortality rates as high as 5% have been reported in patients with EBE from an extraocular infection [4]. Blood cultures remain the most reliable way to establish a diagnosis. These cultures are routinely performed in a hospital setting, and although they are more likely to identify the underlying pathogen compared to intraocular cultures, results can be negative in up to half of cases [3–5, 8, 9]. Intraocular cultures become very important in cases of negative blood cultures. They can be obtained from the anterior chamber by paracentesis (AC tap) or from vitreous collection, either by needle aspiration or during pars plana vitrectomy (PPV). Experimental and clinical studies of exogenous bacterial endophthalmitis have found vitreous cultures to have a higher yield compared to aqueous cultures [10, 11]. It is less clear whether these results apply to EBE eyes. Nevertheless, a review of 342 cases of EBE found anterior chamber samples obtained alongside vitrectomy to be positive in 21% of the cases while a positive vitreous sample was obtained during vitrectomy in 41% of the cases [3]. Yet, AC tap has been advocated to be performed in eyes with more prominent anterior chamber inflammation and when the offending microorganism is still unknown [12]. Moreover, AC tap is a less invasive procedure than vitreous sampling. Due to its high sensitivity, PCR has emerged as an adjunct to cultures in diagnosing EBE. It is capable of amplifying DNA from a single bacterium in a few hours. Hence, it can establish a diagnosis days before culture results become finalized and identify organisms in a culture-negative specimen, even after

antibiotic treatment has been initiated [13–16]. However, PCR has not replaced the utility of traditional cultures. It does not offer any insight into antibiotic sensitivity, which is important for antimicrobial stewardship, and its high sensitivity makes it vulnerable to false positive results from cross-contamination [17]. Nevertheless, due to increased affordability and reproducibility in addition to the aforementioned benefits, PCR is becoming increasingly utilized even in developing countries [18–20].

Regional variations exist regarding bacterial organisms that cause EBE. For example, Gram-positive bacteria comprise the majority of infections in North America and Europe, while Gram-negative organisms predominate in East Asia [1, 5]. This discrepancy can be attributed to *Klebsiella* being the most commonly reported organism behind EBE in East Asia [21]. In fact, up to 90% of EBE cases in East Asia were found to be result of *Klebsiella* spp., likely secondary to the high incidence of DM and hepatobiliary disease in that area [2, 6, 21]. Liver abscess is a common source for *Klebsiella*-induced EBE [2, 7, 22]. Other common Gram-negative species include *Pseudomonas aeruginosa*, *Neisseria meningitidis*, *Escherichia coli*, *Salmonella* spp., and *Serratia marcescens*. Patients with EBE from *P. aeruginosa* commonly have predisposing factors such as cystic fibrosis, immunosuppression, history of lung transplant, and endocarditis [23–25], although EBE by *P. aeruginosa* has been reported in an immunocompetent patient with an unknown source of infection [26]. *N. meningitidis* is also a common pathogen in children with EBE but has been on the decline with the advent of antibiotics [4]. It is important to suspect *N. meningitidis* in patients with sepsis, fever (which can be high and relapsing), rash involving the palms and soles, and meningismus; however, it is not always the culprit [27]. *N. meningitidis* has been isolated from eyes without the classic signs of meningococemia [16, 28–32]. The majority of patients with *Escherichia coli* endogenous endophthalmitis have associated urinary tract infections and renal abscesses<sup>4</sup>. *Salmonella typhi* has been identified as a cause of endogenous endophthalmitis following typhoid fever [33, 34]. One study found that 7 out of 14 patients were under one year of age [33]. Therefore, endogenous endophthalmitis should be suspected in all patients following typhoid fever, especially in infants. Other members of the *Salmonella* spp. have been implicated [35–37]. *Serratia marcescens* is commonly associated with nosocomial catheter-related infections in immunocompromised patients along with urogenital tract infections and IVDU [38–43].

The most common Gram-positive bacteria in EBE are *Staphylococcus aureus*, Group B streptococci, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Enterococcus faecalis*, *Bacillus cereus*, and *Nocardia* species [2, 44]. One study found that *S. aureus* was the single most common organism to cause EBE (25% of cases) [1]. *S. aureus* can be further divided into methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA). The latter group is typically more difficult to treat due to increased antibiotic resistance [45, 46]. MRSA infections are mainly found in hospitalized patients with predisposing risk factors such as DM, HIV, end-stage renal disease (ESRD), IVDU, skin/joint infections, and indwelling catheters; however, it has also been documented in immunocompetent patients without any known underlying risk factor [43, 47–52].

Group B *Streptococcus* endogenous endophthalmitis typically arises by hematogenous spread secondary to pneumonia, pharyngitis, UTIs, and skin infections [53, 54]. The endophthalmitis caused by this organism is commonly associated with endocarditis and septic arthritis [53, 54]. *Streptococcus pneumoniae* was found to be the most common isolated organism (20.8%) in a large Indian study that involved 173 eyes with EBE [55]. Interestingly, the majority of patients with EBE in this study were young (mean age 25 years) and without any predisposing illnesses (~68%). However, patients who are immunocompromised and asplenic, are susceptible to

EBE by this microorganism [56–58]. Endogenous endophthalmitis has also been observed in patients with *S. pneumoniae* meningitis [59, 60].

*Listeria monocytogenes* is a Gram-positive rod that is typically transmitted via ingestion of contaminated food. Chronic uveitis has been documented as a sequela of this bacterial infection and requires long-term topical steroid therapy [7]. Blood cultures (23% positive yield) have significantly lower yield than intraocular tissue sampling such as aqueous (86%) and vitreous (78%) [7]. The source of infection is typically not found [7].

*Enterococcus faecalis* is a natural inhabitant of the GI tract and is a rare cause of EBE. A few documented cases identify some of the sources to be secondary to cholecystitis, indwelling catheter, and prosthetic valvular endocarditis [52, 61, 62]. One case has also been documented after gastrointestinal illness [63].

*Nocardia spp.* are ubiquitous filamentous bacteria found in water, soil, and decaying vegetation. These microorganisms are typically known to disseminate from a pulmonary focus in immunocompromised patients; however, EBE in immunocompetent patients has also been documented [64]. Up to half of patients are transplant patients, and a quarter have underlying autoimmune diseases [65]. Chorioretinal lesions are a common manifestation of *Nocardia* EBE and are believed to be the most frequent bacterial cause of subretinal abscesses [59, 65, 66]. They are found to occur in around 69% of patients, often requiring retinal biopsy and vitrectomy for diagnosis and treatment [65]. *Bacillus cereus* is very common in patients with history of IVDU [60, 67, 68]. Infection by this microorganism is known for its rapidly progressive and explosive course, which can often lead to panophthalmitis [60, 68–70].

### 3. Treatment of endogenous bacterial endophthalmitis

Treatment of EBE has evolved significantly in the last century, particularly after the introduction of antimicrobial agents. Initially, systemic administration was common practice and is still necessary to save the patient's life, but systemic therapy has lower efficacy of saving the eye. It has been established that antibiotic intraocular levels are insufficient to achieve any ocular clinical benefit [71, 72]. It is important to note that despite loss of vision, the infection in the eye should be treated to prevent meningitis and contiguous spread to the surrounding orbital tissues.

In the 1970s, Peyman et al. used animal models to better understand the blood-ocular barrier and to determine non-toxic doses of antimicrobials. They established the use of intravitreal antibiotic injections (IVI) as the standard of care for the treatment of endophthalmitis [73–76]. In the 1990s, the Endophthalmitis Vitrectomy Study (EVS), which studied only exogenous endophthalmitis, established IVI (IVI- of Pharmaceuticals) as standard of care and reported no additional benefit for using systemic ceftazidime and amikacin [77]. Nevertheless, the studied population was post-operative endophthalmitis patients, so the results may not be directly applicable to patients with EBE [77]. Also, they used systemic steroids rather than intravitreal steroids, the latter of which are known to be beneficial in saving visual function by decreasing intraocular inflammatory mediators and the former are questionably prudent in a systemic infection.

Although the treatment of EBE remains controversial due to a paucity of clinical trials, systemic antibiotics remain essential, as many patients have an underlying systemic infection or a distal infectious focus. In fact, in a study that looked at 342 cases of EBE, the two patients who did not receive systemic antibiotics died, while the 51 patients who did receive appropriate systemic treatment survived, although

this was not statistically significant ( $P = 0.10$ ) [4]. Currently, systemic antibiotics are seldom used as a monotherapy but are often used in combination with intravitreal antibiotics, and sometimes PPV [3].

Selection of appropriate antimicrobial agents for IVI depends on several factors, including the patient's allergies, the targeted organism, and antibiotic sensitivity and resistance. The most commonly used antimicrobials in IVI for empiric treatment are vancomycin for Gram-positive and ceftazidime for Gram-negative microorganisms [3]. Amikacin and gentamicin IVI can also be used for Gram-negative microorganisms [4]. A tap-and-inject technique is recommended: An intravitreal tap is initially performed through the pars plana to collect a sample of the vitreous for Gram staining and culture, followed by IVI.

Intravitreal corticosteroids have also been used to counter the inflammatory reaction associated with EBE. Dexamethasone is typically the agent of choice. It has been shown to be safe for all ocular structures up to 4 mg and may reduce the need for repeated antibiotic injections as well as improve visual outcomes [3, 25, 78].

The requirement for surgical intervention is not well established in the treatment of EBE. The EVS recommended PPV for patients with light perception vision, but as mentioned previously, the study involved patients with postoperative bacterial endophthalmitis only [77]. Nevertheless, there are several advantages of performing early vitrectomy on patients with EBE, including removing the infectious material from the vitreous and providing ample material for culture. A large series reported improved visual outcomes and lower rates of eviscerations and enucleation in a group of patients who received vitrectomy *versus* an IVI-only group [3]. For more on endophthalmitis treatment and management, please refer to the final section. [Addendum].

#### **4. Endogenous spirochete endophthalmitis**

Spirochetes are unique bacteria with distinct long helically coiled cells. Members of the phylum Spirochaetes include *Leptospira*, *Borrelia burgdorferi*, and *Treponema pallidum*, all of which are known to cause various systemic and intraocular inflammatory manifestations.

*Treponema pallidum* is the causative pathogen for the sexually transmitted infection syphilis. A recent report by the Centers for Disease Control and Prevention (CDC) has revealed that rates of syphilis are on the rise, particularly among HIV-positive patients and men who have sex with men [79, 80]. This rise in syphilis cases also correlates with an increase incidence of ocular syphilis, which is often the presenting feature of the disease [81–83]. The CDC considers a patient to have ocular syphilis if he/she has been diagnosed with syphilis, regardless of the stage, and any symptoms or ocular signs consistent with syphilis. Syphilis, also known as the “great imitator,” can affect any ocular structure, including the cornea, sclera, uvea, retina, and optic nerve, and is often bilateral, and should be treated as a tertiary syphilis [84, 85].

The most common ocular manifestation of syphilis is generally agreed to be posterior uveitis followed by panuveitis, although some report granulomatous iridocyclitis as being most common [83, 86, 87]. Isolated intermediate and anterior uveitis can also occur [88]. Ocular syphilis can also present with necrotizing retinitis that can mimic acute retinal necrosis (ARN) or progressive outer retinal necrosis (PORN). However, these viral entities tend to progress quickly and are unresponsive to penicillin, whereas necrotizing retinitis secondary to syphilis tends to be slower and responsive to penicillin [89]. Moreover, retinal vasculitis can occur with occlusive manifestations [89, 90]. Patients with ocular syphilis may have

several distinct retinal findings that could assist in diagnosis, such as creamy white preretinal precipitates that can migrate over time [91]. In addition, retinal lesions can heal with minimal retinal pigment epithelium involvement [23]. Acute syphilitic posterior placoid chorioretinitis is also a distinct and rare retinal manifestation of ocular syphilis characterized by discrete oval lesions of the outer retina and the inner choroid [83]. It is believed that these lesions occur secondary to inflammation from direct invasion of *Treponema pallidum* of the choriocapillaris, deposition of immune complexes, or a combination thereof [90]. Nevertheless, ocular syphilis is uncommon and constitutes a small percentage (1%–5%) of ocular inflammation cases in tertiary referral centers [80, 88, 92, 93].

One study examining 453 patients in an HIV clinic found incidence of syphilis to be 7.3%, of which 9% had ocular manifestations [94]. HIV-positive patients also showed higher rates of concurrent ocular syphilis at a younger age than immunocompetent patients [84, 88, 95]. Moreover, several studies have demonstrated that HIV-positive patients are more likely to have isolated anterior uveitis than HIV-negative patients [88, 96]. Therefore, the CDC recommends that all patients with HIV should be screened for syphilis, and all patients with syphilis should be screened for HIV. Screening for other common sexually transmitted diseases such as gonorrhea and chlamydia should also be performed. HIV-positive patients are more likely to present with acute, bilateral uveitis with more aggressive ocular involvement than HIV-negative patients [84, 85]. However, the CD4 count has not been shown to affect the frequency of ocular syphilis in HIV-positive patients [97].

Diagnosis of syphilis is achieved by nontreponemal and treponemal tests. Nontreponemal tests include Venereal Disease Research Lab (VDRL) and rapid plasma reagin (RPR) tests, which are commonly used for screening. These tests are sensitive but not specific; therefore, a positive result must be confirmed with a treponemal test such as fluorescent treponemal antibody absorption test (FTA-ABS), *T. pallidum* particle agglutination test (TPPA), or microhemagglutination-*T. pallidum* test (MHA-TP) due to their high specificity [98]. In very early or late stages of the infection, RPR can be negative, therefore, a more sensitive test such as enzyme immunoassay (EIA) or chemiluminescence immunoassays (CIA) can be used instead [99].

Ocular syphilis is categorized as a subtype of neurosyphilis and should receive prompt treatment, as delay in treatment may result in visual loss. Only 12% of patients diagnosed with neurosyphilis were found to have ocular involvement, and syphilitic meningitis does not always accompany ocular syphilis [97, 100]. Nevertheless, the CDC recommends a lumbar puncture to be performed on all patients with syphilis and ocular complaints, even in the absence of clinical neurological findings. Commonly, CSF-VDRL is the initial test followed by CSF-FTA-ABS if the former test is positive [101].

The recommended treatment by CDC for ocular syphilis includes intravenous aqueous crystalline penicillin G, 18 to 24 million units per day administered as 3 to 4 million units every four hours or continuous infusion over 10 to 14 days. An alternative regimen, if patient compliance is guaranteed, is 2.4 million units of intramuscular procaine penicillin G once daily in addition to 500 mg oral probenecid four times a day, both for 10 to 14 days.

*Borrelia burgdorferi*, the culprit behind Lyme disease, is another spirochete known to affect ocular structures. Like syphilis, Lyme disease progresses through different stages. Follicular conjunctivitis occurs in the early stage of the disease (7–11% of patients), while keratitis, episcleritis, uveitis, and neuroretinitis tend to occur in the second and third stages [93, 102, 103]. Anterior, intermediate, posterior, and panuveitis have all been reported to occur in Lyme disease, with the intermediate form being the most common one [104, 105]. Retinal vasculitis is also

a common presentation in patients with uveitis [104, 106, 107]. Exudative retinal detachment and macular edema can also occur, along with involvement of the optic nerve such as papillitis and optic neuritis. However, Lyme-associated uveitis is rare. One study conducted in France found Lyme disease to be causative of uveitis in only 7 out of 1,006 cases [104]. Diagnosing Lyme-associated uveitis can be challenging, and it can be difficult to ascertain whether positive serologic testing was incidental in patients with uveitis. A study looking at 430 patients with uveitis found the incidence of positive Lyme serology to be similar to the general population [108]. Serology for Lyme disease without clinical suspicion (presentation of specific Lyme symptoms, tick bite, and/or presence in a *Borrelia burgdorferi*-endemic area) is discouraged due to high false positive rates [109]. The CDC currently recommends a two-step approach to establish the diagnosis [110]: ELISA, to be confirmed with western blot if positive or equivocal. Direct identification of intact spirochetes has also been reported in the vitreous post-vitreotomy [111]. Cultures and PCR of both vitreous samples and urine specimens have also been applied [112–114]. *Borrelia burgdorferi* is highly susceptible to systemic antimicrobial treatment. Oral doxycycline, amoxicillin, and ceftriaxone are routinely used in systemic treatment of Lyme disease [103, 104]. Intravenous ceftriaxone was observed to be more efficacious in treatment of uveitis compared to oral doxycycline, perhaps due to better penetration across the blood–brain barrier [104]. However, an optimal treatment regimen for uveitis remains elusive, and recurrences of uveitis after successful treatment are common. The etiology of such recurrences is unclear, but they are thought to be either a reinfection, relapse of the original infection (due to antibiotic resistance) or an autoimmune reaction. Steroids can be used as adjunct treatment and, in some cases, can be sufficient when used alone [104]. Intravitreal triamcinolone has been used to treat macular edema in Lyme disease [115].

Leptospirosis, caused by the spirochete *Leptospira*, is a common infection in tropical and subtropical areas such as the Caribbean, Central and South America, the Pacific Islands and Southeast Asia [116, 117]. The most common ocular manifestations include subconjunctival hemorrhage, chemosis, and conjunctival hyperemia. Uveitis, retinal vasculitis, retinal hemorrhages, and papillitis can also occur [118]. It is believed that 4–7 days after the onset of leptospirosis bacteremia, the immune system rapidly clears the pathogen from all host tissues except the eye and the brain, as they are somewhat immunologically privileged, resulting in uveitis 3–6 months post-systemic infection [119, 120]. The exact incidence of uveitis is unclear (3–92%) but can vary from anterior uveitis to panuveitis [119, 121]. Inflammation can be intense, leading to a formation of hypopyon. In fact, hypopyon secondary to leptospiral uveitis is the most common cause of hypopyon in tropical counties [119, 120]. Vitritis has been reported to occur in 76% of cases. Snow banking and vitreous precipitates can also occur in a linear pattern resembling the “string of pearls” that is characteristic of sarcoidosis [122]. The microscopic agglutination test is the gold standard for the diagnosis of leptospirosis; however, other tests such as PCR, ELISA, *Leptospira* dipstick test, and microscopic slide agglutination tests have been routinely used [123]. Intravenous penicillin G is typically reserved for severe infections, while oral doxycycline suffices for milder cases [124]. Topical, periocular and systemic steroids have also been used in the treatment of leptospiral uveitis [122].

## 5. Endogenous mycobacterial endophthalmitis

*Mycobacterium tuberculosis*, a rod shaped, aerobic bacterium, is known to infect around one third of the world’s population [125]. Individuals are infected by



inhalation of small airborne droplets containing the mycobacteria. The immune system is usually capable of containing the infection in immunocompetent patients; however, if that protective mechanism fails, mycobacteria are able to disseminate by hematogenous and lymphatic spread and seed in organs beyond the lungs, leading to extrapulmonary tuberculosis (TB) [126]. The eye is one of the organs that can be affected and represents 2–18% of extrapulmonary tuberculosis cases [127, 128]. *Mycobacterium tuberculosis* is an aerobic bacterium that has increased affinity to organs with high oxygen tension. The choroid is one of the tissues with the highest oxygen tension in the human body, making it especially vulnerable to seeding by mycobacteria.

The diagnosis of intraocular tuberculosis can be challenging, as it may have no pathognomonic eye findings. Instead, it has a protean presentation, which can appear similar to non-tubercular infections. Patients with HIV are more likely to develop intraocular TB than HIV-negative patients [3, 126]. However, severe intraocular TB can also occur in healthy individuals, which may cause a delay in diagnosis and treatment resulting in profound visual and organ loss [129, 130].

Uveitis is the most common ocular manifestation and can take the form of granulomatous anterior uveitis (12–36%), intermediate uveitis, posterior uveitis (11–20%) and most commonly, panuveitis (34–42%) [128]. Retinal manifestations can include multi-focal choroiditis, chorioretinitis, serpiginous-like choroiditis and choroidal tubercles [131–136]. Ocular tuberculosis can even be severe enough to cause panophthalmitis [137].

Identifying *M. tuberculosis* from body tissues and fluids is the gold standard for diagnosis. In the case of intraocular TB, this may require a major intervention such as enucleation, which may be clinically undesirable [138–140]. Moreover, most patients with intraocular TB present without signs of systemic manifestation, and tuberculin skin test (TST) can be negative in patients with disseminated TB [141, 142]. A recent review of endogenous TB endophthalmitis found that the majority of patients (63%) did not have a prior history of tuberculosis, and ocular manifestations were their presenting sign [141, 142]. Furthermore, half of the presenting patients denied any systemic symptoms such as fever, chills or hemoptysis prior to presentation at the eye clinic. The most common presenting symptom was decreased vision (90%), followed by pain (58%), eye redness (32%), and proptosis (6.5%), all of which are nonspecific signs [141, 142].

Together, these factors make accurate diagnosis of intraocular TB challenging. Nevertheless, certain ophthalmic findings can increase the likelihood of establishing the correct diagnosis. A study found that broad-based posterior synechiae, retinal vasculitis with or without choroiditis, and serpiginous-like choroiditis demonstrate a high likelihood of intraocular TB being present; however, the absence of these signs does not rule out the disease [143]. Moreover, retinal vasculitis in intraocular TB mainly involves the veins with perivascular cuffing and vitritis, and focal choroiditis lesions tend to be under the vessels [131, 144]. A presumed intraocular TB diagnosis can be made when these signs are present in addition to a positive tuberculosis test such as Tuberculin Skin Test (TST), QuantiFERON-TB Gold, chest radiograph, or computed tomography of the chest.

Being aware of the limitations of each diagnostic test is vital. As mentioned previously, TST can produce false negative results in some patients. These patients typically have anergy as result of immunosuppression or disseminated TB, hence TST should not be used to rule out TB when suspicion is high [145]. Moreover, spiral chest computed tomography is more sensitive in the detection of pulmonary TB and should be used in cases with normal radiography and high suspicion of the disease [146]. PPV can be an important diagnostic and therapeutic intervention, as it was found to have a higher yield than vitreous tap in returning positive for mycobacteria (87.5% vs.

14.3%, respectively) [142]. Moreover, PPV may have a similar role in improving visual outcomes and reducing the possibility of enucleation in intraocular TB as was demonstrated in EBE cases. PCR also has a high diagnostic value and can be more accurate than cultures in diagnosing intraocular TB [142].

In the absence of confirmatory tests such as direct visualization of the mycobacteria, positive response to antitubercular therapy (ATT) supports the diagnosis of presumed intraocular tuberculosis. In fact, any delay in treatment to establish a definitive diagnosis is discouraged. One study found that systemic antibiotics were started in 47.6% of endophthalmitis of unknown etiology cases prior to establishing a definitive diagnosis [142]. Antitubercular therapy comprises a four-drug regimen: isoniazid, rifampicin, ethambutol, and pyrazinamide. The role of steroids as part of ATT remains controversial. Some studies have found that steroids can be effective in reducing TB-associated mortality and recurrences of uveitis as well as treating macular edema [141, 147], while another multi-center study found the use of steroids was associated with higher treatment failure rates [148]. Failure rates were higher when steroid treatment was started prior to initiation of ATT compared to after [148]. Therefore, judicious use of steroids is recommended as part of ATT. In fact, there might be two different pathophysiological mechanisms behind the intraocular inflammation: an active mycobacterial infection of the eye and an immunological response to the pathogen located elsewhere in the body [3, 143]. Thus, steroids may be more beneficial in the latter case. Higher treatment failure rates were also observed in patients with choroidal involvement and associated vitreous haze [148]. Caution and close observation of patients on ATT is required as isoniazid and ethambutol can cause toxic optic neuropathy [149]. Nevertheless, TB-associated endophthalmitis has a very poor outcome. The majority of cases (83.7%) end in either evisceration, enucleation or exenteration of the eye [142]. Of note, this figure is significantly higher than for EBE which is reported to be 20% [3].

Nontuberculous mycobacteria (NTM) have also been shown to cause endogenous endophthalmitis [150]. They can be divided into slow and rapid growers [151]. The latter group comprises the most cases of overall ocular infections and carries worse visual outcomes [152, 153]. However, rapid growers are mainly associated with exogenous endophthalmitis and can occur in healthy individuals [150]. On the other hand, endogenous endophthalmitis is typically secondary to infection by slow growers and occurs almost exclusively in immunocompromised patients. The source of infection is often unknown but disseminated infections have been documented [150, 154]. Some of the NTM slow growers implicated in endogenous endophthalmitis include *Mycobacterium avium* (the most common), *Mycobacterium kansasii*, *Mycobacterium triplex* and *Mycobacterium haemophilum*. A case of a rapid grower NTM, *Mycobacterium chelonae*, has also been documented to cause endogenous endophthalmitis as has the slow-growing *Mycobacterium bovis* [155, 156]. NTM endophthalmitis is often misdiagnosed as fungal or bacterial infection as it can present as a chronic intraocular inflammation [152, 157]. Therefore, an infection by NTM should be suspected in any immunocompromised patient with chronic granulomatous intraocular inflammation and poor response to anti-inflammatory drugs. Guidelines for treatment of NTM infection have yet to be established; however, slow grower NTM can usually be treated by the standard ATT, while rapid grower NTM are more sensitive to macrolides, aminoglycosides and fluoroquinolones [158].

## **6. Endogenous viral endophthalmitis (EVE)**

Viral infections represent a significant cause of posterior segment endogenous endophthalmitis due to their systemic spread, and viruses are more likely than other

organisms to spread via a neuronal pathway. Viral infections can appear as isolated ocular manifestations or as part of a systemic infection. For example, Herpes Simplex virus 1 (HSV-1) and Varicella Zoster virus (VZV) spread via transaxonal route while Cytomegalovirus (CMV) and Epstein Barr virus (EBV) spread via hematogenous route within lymphocytes [159]. Infections causing posterior segment infections can lead to manifestations of the choroid, retina, and vitreous due to their highly vascularized nature [160, 161]. Prompt recognition and treatment can lead to improved visual outcomes in patients, but EVE is often misdiagnosed as non-infectious uveitis, anterior uveitis, or conjunctivitis, leading to poorer outcomes [160].

Patients with EVE often have an underlying immunosuppressed condition, so they should be evaluated for underlying immunosuppression if not already known [65]. DM, corticosteroid use, diminished lymphocyte response, HIV/AIDS, and malignancy can all encourage viruses to proliferate [162]. Patients with a history of travel to endemic areas or close contact with farm animals (particularly swine herders) should be evaluated for EVE [161]. Cases of EVE following systemic Ebola and COVID-19 infections have also been documented [163, 164]. There have been cases of viral endophthalmitis following intravitreal steroid injections that are exogenous in nature [160]. Identifying the common clinical features can aid in the prompt diagnosis of EVE. Common features include photophobia, decreased visual acuity, and eye pain [161]. Other presenting ocular features include conjunctival hemorrhages, peripapillary hemorrhage, narrowing of the inferior retinal vessels, anterior segment inflammation, focal lesion of the posterior pole, vitreous inflammation, occlusive vasculitis, keratic precipitates, chorioretinal scarring, ocular hypertension, and neovascularization [160, 163, 164]. EVE frequently presents as unilateral disease on presentation but can become bilateral as it progresses [160, 165–167].

Successful treatment of EVE requires prompt diagnosis using fluid from a vitreous tap [160]. PCR is the main laboratory test that has been effective in establishing diagnosis of viral infection such as HSV, VZV and CMV [160]. One study examined aqueous and vitreous fluid samples for HSV-1, HSV-2, VZV, EBV, CMV, and Human Herpesvirus 6 found PCR to have sensitivity and specificity of 91.3% and 98.8%, respectively in detection of herpes viruses as well as toxoplasma and fungal elements [168]. Viral serology of the vitreous is effective in confirming the pathogen involved in 80–90% of cases [160, 169, 170] and frequently changes the working diagnosis (23%) or confirms an uncertain diagnosis (39%) [170]. Moreover, PCR sensitivity can be further improved when combined with the calculation of Goldmann-Witmer coefficient (GWC) and immunoblotting for ocular fluid and serum antibodies. The GWC is a comparison of specific antibodies levels to total immunoglobulin in both aqueous humor and serum samples. Multiplex PCR allows testing of several organisms from a single ocular sample; however, this process, similar to monoplex PCR, does require the knowledge of a particular virion's sequence information prior to testing in order to design the primer necessary to generate a PCR product [171]. Fundus photography, retinal imaging, and optical coherence tomography (OCT) are all useful in diagnosing and monitoring EVE [160, 172].

Treatment of EVE requires systemic antivirals, intravitreal antivirals (or intra-ocular antiviral implants), and systemic corticosteroids for inflammation [160]. In the 1990s, Peyman and many others noted improvement of cytomegalovirus (CMV) retinitis after treatment with intravitreal ganciclovir and systemic antivirals [76, 173–179]. Studies also confirm the efficacy of systemic valaciclovir for appropriate management of EVE [179]. The role of systemic and intravitreal acyclovir for treatment of herpes virus retinitis has also been documented [174, 178]. Management of both ocular and systemic complications is essential for a favorable

prognosis [160]. Long-term preventative antiviral therapy may be considered if patients present with recurrent inflammation. Patients may require anti-vascular endothelial growth factor agents for macular edema or neovascularization [160] and may also undergo vitrectomy for proper management. Vitrectomy should be considered when patients present with severe inflammation, retinal detachment, or traction that may create a detachment. Vitrectomy with silicone-oil tamponade and scleral buckle placement has been proven successful [179]. Caution should be taken in eyes of patients with a history of Ebola virus disease who present with evolving dark retinal regions, as these are characteristic of viable *Zaire ebolavirus* (EBOV) which poses a significant health risk during intraocular procedures [163]. Some eyes may experience neovascularization, for which they should undergo photocoagulation and/or retinal detachment surgery [160].

Several viruses have been implicated in the development of EVE. Most commonly, it is due to reactivation of the herpesvirus family, specifically varicella zoster virus (VZV), herpes simplex virus (HSV I and HSV II), CMV, and Epstein–Barr virus (EBV) [160, 180, 181]. The outcome of viral reactivation is influenced by multiple factors including strain virulence, human leukocyte antigen, and host immune response. HSV- EVE is generally well treated with systemic antiviral and corticosteroids with the resolution of symptoms [181]. However, as the virus remains latent in the trigeminal and dorsal root ganglion, recurrence is possible [181]. VZV-EVE may occur in adults with chickenpox but is rare in children [160]. It is more common in adults and may precede shingles in immunocompromised patients, but Acute Retinal Necrosis (ARN) can occur in patients with normal immune function; HSV I, HSV II, and VZV can cause ARN [182]. VZV generally has a poorer prognosis compared to HSV. EBV-EVE generally has a good prognosis and resolves rapidly with near-complete recovery [160]. Most people (90%) are CMV seropositive (it is thought to be latent in bone marrow) so it periodically actively replicates in both immunocompromised and normal patients. Therefore, culture of CMV shed in the patient's urine does not mean active systemic CMV infection to support the diagnosis of CMV retinitis. Patients can experience systemic symptoms, but ocular manifestations are more likely to be the initial finding [183]. CMV retinitis has historically had poor visual outcomes, although new antiretroviral therapies have decreased its incidence and improved outcomes [183]. Patients may experience reactivation of herpesvirus infections following other viral infections, such as COVID-19 [184].

Other causes implicated with EVE include pseudorabies, Zika virus, Dengue, Ebola, Chikungunya, and COVID-19 [163–165, 185]. Unlike herpesvirus infections, patients typically do not present with a history of immunosuppression. However, history is significant with respect to travel to endemic areas or known exposure to infected individuals [163–165, 185]. The posterior vitreous cavity may act as a reservoir for some viral infections. Zika and COVID-19 infections are notable for the presence of viral RNA in the tears [165]. In contrast, patients with Ebola Virus Disease (EBD) in the eye are negative for Ebola of the tears and conjunctiva [163]. However, virions have been recovered from the anterior chamber in eyes of recovered Ebola patients and poses a risk for cataract surgeons [163].

Patients with ocular viral infections are also at risk for reactivation of other bacterial or fungal agents in the eye. Cases of toxoplasmosis following Ebola infection have been documented in a small subset of patients [127]. Compared to more common causes, novel causes of EVE (Dengue and COVID) have no prospective, randomized therapeutic trials. As such, definitive therapies are not well established, and prognosis can range from full resolution to permanent vision loss [165, 185]. COVID-19 and Zika are more likely to cause poor visual outcomes compared to standard causes [164, 165]. Prompt diagnosis and early treatment are important for good visual outcomes of EVE.

## 7. Endogenous fungal endophthalmitis (EFE)

Fungi can lead to infection of the posterior chamber through hematogenous spread; in fact, this represents the most frequent cause of EFE [186, 187]. Most cases of fungal endogenous endophthalmitis have a predisposing systemic risk factor. Common risk factors for EFE include recent hospitalization, systemic surgery, indwelling catheter, broad-spectrum antibiotic use, steroids, parenteral nutrition, cytotoxic therapies, and gastrointestinal disease [186]. Lower abdominal procedures, including genitourinary procedures (e.g. uterine curettage, urinary tract dilation, lithiasis removal), and toe-nail extraction due advanced onychomycosis have been implicated with EFE [188]. Most cases of fungal endogenous endophthalmitis have a predisposing systemic risk factor [189]. Diagnosis of EFE is frequently missed, as these characteristic findings might mimic non-infectious uveitis and orbital cellulitis [190]. In the pediatric population, common misdiagnoses are orbital cellulitis, congenital glaucoma, conjunctivitis, and retinoblastoma [191]. Misdiagnosis rates range from 16% to 63% [4, 191].

Patients who experience misdiagnosis can experience a delay in diagnosis (mean of 13 days) [186, 192], but familiarity with the clinical features of EFE can aid in avoiding this. Patients frequently complain of blurry or decreased vision (77%), redness (49%), eye pain (34%), floaters (26%), and photophobia (12%) [192]. Systemic symptoms also include frequently mild and relapsing fever, scalp lesions, and other pain [193]. In a study that examined 65 eyes with EFE found most eyes to have diffuse anterior and posterior segment inflammation (71%), followed by focal posterior inflammation (28%) and focal anterior segment inflammation (2%) [186]. Eyes with EFE can have some characteristic exam findings that can help in establishing a proper diagnosis. For example, eyes with EFE from *Candida spp.* typically will have one or more creamy, white chorioretinal lesions most commonly found in the posterior pole [194]. These lesions tend to be less than 1 mm in diameter with an overlying vitritis. Moreover, fluffy white vitreous opacities connected by strands of inflammatory material (“string of pearls”) can be noted [194]. Also, EFE from *Aspergillus* can have a characteristic macular chorioretinal lesion that can be associated with a gravitational layering of inflammatory exudates (pseudohypopyon) either in the preretinal or subretinal space [195].

Due to their systemic nature in immunocompromised patients, cases are more likely to be bilateral compared to other causes of endogenous endophthalmitis, but the majority are still unilateral [196]. Unlike bacterial causes, EFE is less associated with a known focal systemic lesion. About 44% of patients with EFE from *Candida spp.* had no known focal lesion [29]. However, patients frequently present with a history of IVDU, chemotherapy, DM, abdominopelvic procedures and renal failure. Mold infections, caused by organisms such as *Aspergillus*, commonly occur with a history of iatrogenic immunosuppression, corticosteroid use, neutropenic patients, or solid organ transplantation [188, 189, 196, 197]. It is rare for patients with AIDS or IVDU to have *Aspergillus* endophthalmitis [197], and those patients are more likely to have a history of pulmonary aspergillosis or disseminated aspergillosis [196].

An accurate diagnosis of the causative agent is essential to the treatment of EFE. Culture positivity for *Candida spp.* EFE rates range from 45% to 74% in the immunocompromised, perhaps leading to more frequent misdiagnosis in this population. PCR is increasingly becoming the gold standard diagnostic tool for the identification of EFE infections: Identification has been reported to be up to 100% compared to 37.5% in traditional culture techniques [198, 199]. However, PCR does experience the same pitfalls in the diagnosis of fungal infections as it does for EBE. Prompt diagnosis with PCR and intervention with early vitrectomy and/or chorioretinal biopsy have improved patient visual outcomes [200].

*Candida* spp. infections represent the most common cause of fungal endogenous endophthalmitis, with incidences ranging from 34–36% of cases of all EFE [29]. The *Candida* spp. are known to affect the eye and have a predilection toward the posterior segment [190, 196]. Reports show infection of *Candida* spp. after pace-maker implantation [196]. In immunocompromised patients, the most common cause of fungal endogenous endophthalmitis is *Candida* [199]. Infection with a new candida strain, *Candida dubliniensis*, has been noted in several countries. Although much less frequent than other *Candida* species, *C. dubliniensis* can present with fluconazole-resistance and no other systemic evidence for disseminated disease [201]. However, *C. dubliniensis* has better treatment outcomes compared to *C. albicans* [201]. Despite its low frequency in overall endophthalmitis cases, *Candida albicans* is the most common cause of endogenous endophthalmitis in pediatric populations worldwide. Risk of infection increases with a history of distant wound infection, meningitis, intravenous catheters, and UTIs [191, 202]. Common causes of pediatric fungal endophthalmitis include neonatal sepsis, poor hygiene, or an immunocompromised status [191]. Given the high rates of misdiagnosis in this population (63%), there is evidence that dilated ophthalmic examination of patients with invasive fungal disease and screening of at-risk children with evidence of fungal colonization has some therapeutic benefit [4, 191, 203].

The *Aspergillus* genus represents the second most common cause of fungal endophthalmitis (33%) [199]. Other common opportunistic fungi include *C. neoformans*, *Fusarium* spp., *Scedosporium*, *Rhodotorula* spp., *Mucor* spp., *Alternaria* spp., *Acremonium falciforme*, *Pneumocystis jiroveci*, and many other less prevalent fungal species [167, 196, 198, 204]. Microsporidium has also been implicated with posterior segment etiology [205].

Pathogenic dimorphic fungi have also been implicated in EFE. Unlike opportunistic causes, pathogenic dimorphic fungi are usually regionally restricted. These infections can cause endophthalmitis in both immunocompetent and immunocompromised hosts. EFE is primarily a result of a disseminated pulmonary infection [196, 206]. Examination of the eye for dimorphic fungi shows fluffy yellow/white aggregates with retinal hemorrhages. *Coccidioides immitis*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *S. schenckii* have all been implicated as regional causes of EFE [167, 196, 198, 204]. Patients who are suspected of having systemic *C. immitis* and *Blastomyces* should undergo serial eye examination given its insidious nature, especially for immunocompromised patients [196, 207, 208]. *C. immitis* does not always present with signs of systemic infection, so visual cues such as vitreous opacities are beneficial to a systemic diagnosis [207]. Despite early diagnosis and prompt treatment, it is reported that 50% of patients who do not succumb to the disseminated infection undergo enucleation of the infected eye [196, 207–209]. The initial treatment of suspected EFE should be intravitreal and systemic antifungal agents followed by early surgical intervention [193]. Depending on the specific cause and duration of EFE, medications used for treatment include amphotericin B, systemic fluconazole (oral or IV), voriconazole, and caspofungin, with preference depending on sensitivity of the infection and side effect profile. Like EBE, a tap-and-inject technique is recommended through the pars plana to collect a sample of the vitreous for culture followed by intravitreal injection of antifungals. Again, sometimes a chorioretinal biopsy may be required for identification of the fungus [171, 200, 210].

Treatment of endogenous fungal endophthalmitis in the eyes of pediatric population have shown favorable resolution with systemic and intravitreal antifungals, intravitreal steroids, and early surgical intervention. However, there is no specific guideline for dosing of pediatric patients with EFE with systemic and intravitreal antibiotics. [192]. While patients with EFE have shown resolution of symptoms, as

noted, with systemic and intravitreal antifungal medications, eyes that present with poor vision or are refractory to injected antifungals should undergo vitrectomy [198]. Surgical intervention via early PPV has been proven to have therapeutic efficacy [199].

Of all the fungal causes, infections with *Candida* spp. have shown the best visual acuity outcomes. Results for eyes with *Aspergillus* EFE are not as favorable because of increased rates of macular scarring secondary to infection [211].

## 8. Endogenous protozoal endophthalmitis

Protozoans, unicellular eukaryotic organisms, are a major cause of intraocular infections worldwide. Different protozoa have special animal hosts with varying routes of infection. Travel and dietary history as well as patient habits are important in establishing a diagnosis, since most transmission occurs through contaminated food and water sources in endemic areas. Protozoa such as *Giardia lamblia*, *Plasmodium falciparum*, *Acanthamoeba* spp., and *Toxoplasma gondii* can all present with intraocular manifestations; however, only toxoplasmosis is well established to cause endogenous endophthalmitis.

*Acanthamoeba* spp., typically associated with contact lens wear, trauma, and contaminated water exposure, can cause keratitis. Advanced stages can lead to corneal perforation and endophthalmitis; however, it is exogenous in nature secondary to direct corneal extension [212, 213]. Malaria, an infectious disease caused by *Plasmodium* and carried by *Anopheles* mosquitoes, leads to retinal ocular manifestation without any intraocular inflammation. Retinal findings, such as patchy retinal whitening and retinal hemorrhages, occur in severe cerebral malaria caused by *Plasmodium falciparum* but are secondary to microvascular obstruction and severe anemia [214, 215]. *Giardia lamblia*, the most common intestinal parasite worldwide, is acquired through ingestion of cysts from contaminated water [216]. Asymptomatic salt-and-pepper retinal degeneration is the most common ocular manifestation of giardiasis [217]. Only rare cases of retinal arteritis and anterior uveitis have been documented in the literature [218, 219]. Ocular sequelae of giardiasis is believed to occur as result of immune response to cross-reacting antigens or molecular mimicry rather than a direct invasion by the parasite [217, 220].

*Toxoplasmosis gondii*, a ubiquitous protozoan that infects roughly one third of the human population, is the most common cause of uveitis worldwide [221, 222]. Oocytes from cat (definitive host) feces infect humans (intermediate hosts) through consumption of contaminated water and undercooked meats (animals already infected) or from direct mishandling of domestic cat feces [223, 224]. In the past, all cases of ocular toxoplasmosis were believed to be reactivations of previous congenital infections; however, recent evidence has shown that most cases are in fact acquired postnatally [221, 225]. Congenital infection occurs when the mother is infected with the protozoa either just before conception or during gestation, which leads to vertical transmission through the placenta to the fetus. Fetal transmission only occurs if the mother is exposed to the parasite for the first time or to a novel strain [226]. Unless she is immunocompromised, a previously infected mother already possesses the immunity that protects her and the fetus from any new infection. Fetal infection during the first trimester will typically lead to a more severe form of congenital toxoplasmosis than later stages of pregnancy [227]. Retinochoroiditis is a common ocular manifestation, which may lead to blindness if left untreated [228]. Other extraocular clinical signs of congenital toxoplasmosis include seizures, sensorineural hearing loss, intracranial calcifications, microcephaly, and cognitive impairment. Prompt treatment of the newly infected mother

with spiramycin has demonstrated a 60% reduction in congenital toxoplasmosis [229]. Moreover, prompt postnatal treatment of infants is also warranted. Infants who were treated after one year of life were more likely to develop new retinochoroidal lesions than patients who received earlier treatment (70% vs. 31%, respectively) [230]. It is important to note that clinical presentation of congenital toxoplasmosis can resemble congenital viral infections such as HSV, CMV, Zika virus, and rubella, which needs to be taken into consideration when making the diagnosis [228].

Other clinical classifications of toxoplasmosis include acquired cases in immunocompetent and immunocompromised patients. Toxoplasmosis is mainly asymptomatic in healthy patients. Painless cervical lymphadenopathy is the main clinical manifestation if symptoms do occur. Retinochoroiditis is also a common feature, since *Toxoplasma gondii* is the most common pathogen to infect the retina in immunocompetent patients [231]. Retinal lesions can present in acute or reactivation stages, and in the latter case, lesions are essentially similar whether the original infection was congenital or acquired [232, 233].

Retinochoroiditis is frequently subclinical but can result in retinal detachment and loss of vision [228, 234]. Other symptoms may include pain, photophobia and epiphora. Ophthalmic exam is vital in the diagnosis of retinochoroiditis, which typically presents as a focal white lesion with overlying vitritis. When vitritis is severe, a classic finding of “headlight in the fog” can be seen. Healed lesions become atrophic and develop a scar bordered with black pigment. Atypical lesions found in elderly and immunocompromised patients have distinctive characteristics including hemorrhages, multiple foci and features present in acute retinal necrosis (ARN) such as peripheral retinitis, vasculitis and vitritis [235, 236]. Early management of toxoplasmosis in immunodeficient patients is vital, as disseminated disease has 100% mortality if left untreated.

Recurrences of retinochoroiditis are common, roughly 80%, with a median interval of two years [237]. New lesions tend to occur at the border of an old, scarred lesion. Recurrences are more common after cataract extraction and in patients older than 40 years of age as well as in previously affected eyes [237–239]. Nevertheless, late sequelae and recurrences from congenital infection tend to be bilateral, more severe, and involve the macula, whereas acquired infections are usually unilateral, spare the macula, and are not associated with an old chorioretinal scar [228, 232, 240].

The diagnosis of toxoplasmosis is mainly clinical based on characteristic retinal lesions; however, serology can confirm the exposure to the protozoa. Various methods exist for detecting IgG and IgM immunoglobulins against *Toxoplasma gondii* such as immunocapture, immunoblot, immunosorbent agglutination, indirect immunofluorescence, enzyme-linked immunosorbent assays, and Chemiluminescence Immunoassay (CLIA) [241–243]. Each test has its own sensitivities and specificities which are beyond the scope of this chapter. Nevertheless, IgM antibodies indicate a primary infection and can be especially helpful in pregnant patients to determine whether infection occurred during or prior to pregnancy, while memory IgG antibodies demonstrate previous infection. IgM antibodies typically appears during the first week of infection and can remain detectable up to a year, while IgG appears approximately 2 weeks after the infection and typically remains detectable for life [244]. For example, patients with chronic and recurrent retinochoroiditis will typically only have IgG detected, whereas detection of both IgM and IgG typically indicates a primary and acute infection.

These serological tests only reveal previous exposure to *Toxoplasma gondii* and offer little insight into the mode of transmission. However, a new test using a protozoa-specific protein called *T. gondii* embryogenesis-related protein (TgERP)



can be useful in determining the original source of infection [245]. PCR amplification has also been successfully utilized in the diagnosis of toxoplasmosis and can be especially useful in atypical patient presentations. PCR is also beneficial in testing for congenital infections, since it offers earlier diagnosis and avoids the invasiveness of serum testing on fetuses by sampling amniotic fluid [228, 246]. PCR can also utilize CSF, urine, fetal, and placental tissue [228, 247]. Moreover, a newer test that utilizes similar general principles of PCR, known as loop-mediated isothermal amplification method (LAMP), might offer a cheaper and simpler alternative in confirming *Toxoplasma gondii* exposure [248].

There is a lack of evidence supporting the utility of routine antibiotic and steroid regimens in the treatment of acute retinochoroiditis [249]. Not all cases necessarily warrant treatment; for example, small lesions in the periphery that are not vision-threatening tend to be self-limited and will heal spontaneously in immunocompetent patients [250–252]. Most clinicians will treat patients with disease persisting more than one month and associated with reduced visual acuity. Other indications for treatment include lesions that are vision-threatening such as those affecting the macula or the optic nerve, lesions larger than one disc diameter, lesions in monocular patients, presence of multiple lesions, lesions associated with moderate to severe vitritis, active lesions over a large vessel, or lesions in immunocompromised patients [253]. The classic triple therapy comprises oral pyrimethamine, sulfadiazine, and prednisolone. Pyrimethamine is prescribed with folinic acid to prevent bone marrow toxicity (anemia). Alternative treatments include oral trimethoprim-sulfamethoxazole (TMP-SMX), azithromycin, or clindamycin, all of which have shown favorable results [254–256]. Intravitreal treatment has also been studied for the treatment of ocular toxoplasmosis [257, 258]. Combined clindamycin and dexamethasone intravitreal injections were found to be comparable to a regimen of oral pyrimethamine and sulfadiazine [258–260]. Intravitreal TMP-SMX with dexamethasone also demonstrated benefit [261, 262]. Intravitreal injections can be favorable in pregnant patients due to their reduced systemic toxicity compared to oral medication [263, 264]. Photocoagulation around the foci of the scars and vitrectomy have also been performed; however, these studies are limited and did not show any preventive effect [265]. Fulminant ocular toxoplasmosis may occur with corticosteroid monotherapy, in which case vitrectomy may be warranted [266].

## 9. Endogenous helminthic endophthalmitis

Helminths at either the larval or adult stage can lead to the infection of ocular tissues through adjacent structures or may have a predilection for ocular tissue as they migrate through the vascular system [267]. Helminths generally only have a unilateral eye presentation, but there is no observed difference in eye predominance [192]. Although infrequent, helminth infections are more common in areas of consumption of contaminated water, raw meat, and freshwater fish [268, 269], so travel history to endemic areas is essential to ascertain the source of the infection. However, due to movement via rapid transport, such history might not be present [267]. Helminth endogenous endophthalmitis is much less frequent compared to bacterial, viral, and fungal causes. Pediatric populations are more likely to have zoonotic infections, such as *Toxocara canis*, due to ingestion of eggs or larvae in the feces of infected animals [270]. As such, rates for infections from parasitic sources are higher than the adult population [192] and more likely to be from less virulent organisms [192]. A common misdiagnosis in pediatric patients with an ocular helminth infection is retinoblastoma, requiring enucleation of the eye [192].

Due to the nature of these parasites, pathological lesions show a wider variety of clinical presentations compared to other causes of EE. Perhaps the most common cause of helminth infection is *Toxocara*, a notable cause of unilateral visual loss. Autopsy of affected individuals has shown infection of the brain, eye, lungs, and liver [268–270]. Human infection is noted in populations with a high prevalence of the consumption of freshwater raw fish [271]. Diagnosis of ocular toxocariasis is mainly a clinical one as the definitive diagnosis of histologic demonstration of larva is unfeasible and rarely done. Ophthalmic presentation of ocular toxocariasis include granuloma located in the posterior pole (25%) or the periphery with associated fibrous bands extending posteriorly (50%) [272]. Chronic endophthalmitis is also a common presentation (25%) [272]. Serum ELISA antibody test is commonly used to detect exposure to toxocariasis; however, intraocular fluid (aqueous humor and vitreous) ELISA antibody testing can be positive despite negative serum [270, 272]. Systemic or topical corticosteroid is commonly used to control the acute inflammatory reaction [270]. Albendazole is the current antihelminth drug of choice; however, it has yet to be proven that antihelminth drugs can kill intraocular larva [273, 274]. Pars plana vitrectomy or laser photocoagulation to remove the causal agent is also recommended in some patients [268, 270].

Two helminths with ocular manifestations are *Onchocerca volvulus* and *Loa loa*. Humans with an *Onchocerca volvulus* infection generally have an adult worm that produces microfilariae over a bony prominence. The microfilariae migrate throughout the connective tissue, skin, and ocular structures. Predominant ocular findings include punctate keratitis, iridocyclitis, chorioretinitis, and optic atrophy [268]. Diagnosis is accomplished via slit-lamp examination of microfilariae, with the aid of a punch biopsy [268, 275]. Treatment includes removal of the adult worm and administration of ivermectin. *Loa loa* is also diagnosed via circulating microfilariae; however, the adult worm is more commonly found in the conjunctiva [268]. Treatment of *Loa loa* includes removal of the worm and use of diethylcarbamazine [268]. Another helminth involved in EE is *Angiostrongylus cantonesis*. Patients generally present with blurred vision and poor visual acuity, and ocular symptoms generally occur two weeks to two months after ingestion of the *Pila* snail [268]. Patients are diagnosed via indirect ophthalmoscopy. Patients generally do not have favorable outcomes with an ocular infection of the nematode *Angiostrongylus*. Surgery, laser, and corticosteroid interventions do not improve visual acuity, as alteration of the RPE and retina are caused by the parasite directly. There is no specific therapy for *Angiostrongylus* EE [268]. Many other helminth infections have been implicated in endogenous helminth endophthalmitis, including dirofilariasis, taenia solium, fascioliasis, and schistosomiasis [268, 276, 277].

One helminth unique to the pediatric population is *Baylisascaris procyonis*, a raccoon roundworm originating in North America. Seven cases document children with a history of pica and raccoon exposure who developed unilateral subacute neuroretinitis [278]. The worm can be identified via immunofluorescence assay of the serum or CSF, but the definitive diagnosis is visualization of the offending organism in the eye. Treatment options include albendazole and corticosteroids, but patients have a poor prognosis [279].

The most common helminths in the pediatric population are *Toxocara* and *Cysticercus*. Pediatric infections generally have fewer systemic symptoms, causing a delayed diagnosis of endogenous endophthalmitis [192]. Results in pediatric populations are not as favorable as in adult populations due to the delay in diagnosis and diffuse infection of the eye. Advantages of an early vitrectomy in pediatric populations include improved outcomes in patients, though visual rehabilitation is still a challenge for this population [192].

Helminths have also shown surprising manifestations in immunocompromised hosts. One patient with a history of systemic lupus erythematosus (SLE) presented with decreased bilateral vision in both eyes. Fundoscopy showed granulomas in the posterior poles bilaterally, with new granulomas developing in subsequent exams. Serology was positive for *Toxocara*. The patient was initially treated with intravitreal amphotericin B, vancomycin, and ceftazidime. After a full course of antibiotics and with albendazole, the patient had improved visual acuity of both eyes [280].

Another subset of immunocompromised patients who are at risk for helminth-induced endogenous endophthalmitis is the IVDU population. One patient with a history of IVDU reported two weeks of worsening right eye pain with decreased visual acuity. Endophthalmitis was suspected and a vitreous tap was performed. Gram stain showed no organisms, but rare white blood cells were present. Initial labs, bacterial and fungal cultures were negative. The patient was admitted for the endogenous spread of infection and placed on IV antibiotics. The patient's repeat serology was found to be positive for *Toxocara* titers [269].

Diagnosis of *Toxocara* or other helminths can be difficult in immunocompromised patients. Presentations can vary from granuloma formation to chronic retinal manifestations [269, 280]. Additionally, the parasitic load may not be high enough to give a positive serology result [269]. Serial optical coherence tomography (OCT) to observe for larval movement might aid diagnosis.

Immunocompromised patients with significant animal contact who present with suspicion of endogenous endophthalmitis should be considered for a helminth cause [4, 9]. Treatment of ocular toxocariasis should be tailored to the clinical presentation of the host, and patients with inflammation should be placed on steroids to reduce the risk of retinal detachment. Anti-helminthic agents and IV antibiotics have been successful, but surgical intervention may be necessary if complications occur [280].

## 10. Conclusion

Endogenous endophthalmitis can be a result of a systemic infection from a myriad of infectious agents including bacteria, viruses, fungi, protozoa, and helminthic organisms. Systemic infection should be suspected when there is no history of surgical intervention or trauma. Unlike exogenous endophthalmitis, the onset of clinical manifestations may be insidious and difficult to diagnose. This is particularly true in nonverbal patients.

<b>Amikacin 200 µg per 0.1 ml</b>	<p>Step 1: Withdraw 0.4 ml from an amikacin vial (100 mg/2 ml)</p> <hr/> <p>Step 2: Add the step 1 solution to a second 10 ml syringe containing 9.6 ml &lt; 0.9% NaCl for injection USP (Preservative Free)</p> <hr/> <p>Step 3: Withdraw 0.1 ml from step 2 solution (2 mg/ml), which will now contain 200 µg/0.1 ml of amikacin</p>
Ceftazidime 2.2 mg/0.1 ml	<p>Step 1: Reconstitue 1000 mg ceftazidime powder with 8 ml of 0.9% NaCl for injection USP (Preservative Free)</p> <hr/> <p>Step 2: Withdraw all 8 mL of that the solution prepared in step 1 and add saline to create total volume of 10 ml. Then, withdraw 1 ml of that solution in a second syringe with 3.5 ml of 0.9% NaCl for injection USP (Preservative Free) (Total volume 4.5 mL)</p> <hr/> <p>Step 3: Withdraw 0.1 from the step 2 solution (22.2 mg/ml), which will now contain 2.2 mg/0.1 ml of ceftazidime</p>

Amikacin 200 $\mu\text{g}$ per 0.1 ml	Step 1: Withdraw 0.4 ml from an amikacin vial (100 mg/2 ml)
	Step 2: Add the step 1 solution to a second 10 ml syringe containing 9.6 ml < 0.9% NaCl for injection USP (Preservative Free)
	Step 3: Withdraw 0.1 ml from step 2 solution (2 mg/ml), which will now contain 200 $\mu\text{g}$ /0.1 ml of amikacin
Clindamycin 450 $\mu\text{g}$ /0.1 ml	Step 1: Withdraw 0.3 ml from a vial of clindamycin (150 mg/ml)
	Step 2: Add the step 1 solution to a second 10 ml syringe containing 9.7 ml of 0.9% NaCl for injection USP (Preservative Free)
	Step 3: Withdraw 0.1 ml from step 2 solution (4.5 mg/ml), which will now contain 450 $\mu\text{g}$ /0.1 of clindamycin
Gentamicin 100 $\mu\text{g}$ /0.1 ml	Step 1: Withdraw 0.25 ml (10 mg) from a gentamicin vial (40 mg/ml)
	Step 2: Add the above 0.25 ml to a new 10 ml syringe containing 9.75 ml of 0.9% NaCl for injection USP (Preservative Free) (Final concentration 1mg/ml)
	Step 3: Withdraw 0.1 from step 2 solution (1 mg/ml), which will now contain 100 $\mu\text{g}$ /0.1 ml of gentamicin
Vancomycin 1 mg/0.1 ml	Step 1: Dilute a vial of vancomycin powder (500 mg) with 10 ml 0.9% NaCl for injection USP (Preservative Free) Final concentration (50 mg/ml)
	Step 2: Withdraw 1 ml solution prepared in step 1 (50 mg/ml) into a new 5 ml syringe and add 4 ml of 0.9% NaCl for injection USP (Preservative Free) Final concentration (10 mg/ml)
	Step 3: Withdraw 0.1 from the step 2 solution (10 mg/ml), which will now contain 1 mg/0.1 ml of vancomycin
Dexamethasone 1000 $\mu\text{g}$ (can inject to 1 mg)	Step 1: Withdraw 0.1 ml from a dexamethasone vial up containing 10 mg/ml vial
Amphotericin B 5 $\mu\text{g}$ /0.1 ml	Step 1: one vial of 50 mg amphotericin B is diluted with 10 ml of sterile water (Preservative Free) Final concentration (5 mg/ml = 0.5 mg/0.1 ml)
	Step 2: Withdraw 0.1 ml of step 1 solution (0.5 mg/0.1 ml) and add it to 9.9 ml of sterile water (Preservative Free) Final concentration (0.05 mg/ml)
	Step 3: Withdraw 0.1 ml from step 2 solution, which will now contain 5 $\mu\text{g}$ /0.1 ml of amphotericin B -final concentration 0.005mg/0.1 ml

**Table 1.**  
 Preparation of intravitreal pharmaceuticals.

1. Anesthetize the eyes with a topical anesthetic
2. Sterilize the eye with 5% povidone-iodine solution
3. Using a 25-gauge needle attached to a tuberculin syringe, position the needle perpendicular to the eye wall and enter 3.5 mm (in pseudophakic or aphakic eyes) or 4 mm (in phakic eyes)
4. Ensure the visualization of the needle from the pupil prior to aspirating the sample.
5. Gentle aspiration without excessive pressure then withdraw the needle.

Pearl 1: If 25-gauge needle is unsuccessful in obtaining a sample, then a 23-gauge needle can be used after making a small sclerotomy but a safer way is to use a 25 gauge vitrector through the sclerotomy site to obtain vitreous samples.

Pearl 2: Avoid attaching antibiotics to the original vitreous biopsy needle while in the eye due to increased risk of retinal injury. It is preferred to withdraw the biopsy needle and re-enter the eye with a new needle for antibiotic delivery.

Pearl 3: Injection of drugs should be limited to the smallest possible volume and the bevel of the needle

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should be placed toward the lens, not toward the retina w.

Pearl 4: Do not combine dexamethasone and vancomycin in the syringe due to precipitation, but aminoglycosides and dexamethasone can be used in the same syringe. Of note, hemorrhagic occlusive retinal vasculitis has been reported with intravitreal gentamicin treatment

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**Table 2.**

*Vitreous tap technique [265].*

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- We recommend performing a PPV when endophthalmitis is suspected and when vitreous haze precludes the view of the disc or a large vessel.
  - Goal of the PPV is to remove vitreous debris, obtain adequate sample for culture, reduce bacterial load, and prevent any further enzymatic degradation of the retina.
- 

**Table 3.**

*Pars Plana vitrectomy role Endophthalmitis [265].*

- 
1. In the absence of posterior view, we recommend insertion of a bent 23-gauge needle to infuse sterile air or balanced saline solution (BSS).
  2. Resort to 23-gauge pneumovitrector or 25-gauge vitreous microinstrumentation to obtain diagnostic vitreous samples. These two instruments lead to minimal traction on the peripheral retina during vitreous collection.
  3. In order to maintain IOP without sample dilution, the infusion fluid can be turned on as soon as the vitreous sample has been collected.
  4. The vitrector aspiration port is attached to sterile syringe. Manual aspiration is applied as the surgeon performs the vitreous biopsy.
  5. Lighted infusion cannula can be used as a source of light and infusion during both the vitreous biopsy collection and subsequent vitrectomy.
  6. It is recommended that a separate posterior infusion cannula be placed early in the procedure.
  7. Manipulation close to the retina should be avoided. A complete vitrectomy is not necessary at the first operation.

Pearl 1: Ensure avoidance of the retina in cases where the view is impaired, such as in eyes with a dense cataract.

Pearl 2: Vitrector can be safely placed behind the IOL in pseudophakic eyes.

Pearl 3: We recommend intravitreal and systemic therapy in endogenous endophthalmitis cases, especially in mycotic cases.

Pearl 4: Fluconazole 200  $\mu$  g/ml can be safely used in the infusion fluid during vitrectomy of eyes with endogenous fungal endophthalmitis.

Pearl 5: (*Silicone filled eyes*)

-Vitreous tap should be performed initially followed by intravitreal injection of one-quarter the recommended antibiotic dose for non-vitrectomized eye along with 1 mg dexamethasone.

-When purulent exudates are present in the vitreous cavity, we recommend the removal of silicone while using infusion fluid with recommended doses of antibiotics and steroids.

-The recommended infusion fluid composition for EBE: 20  $\mu$  g/ml vancomycin, 9  $\mu$  g/ml clindamycin, 8  $\mu$  g/ml gentamicin, 64  $\mu$  g/ml of dexamethasone.

-Silicone oil can be injected immediately after removal of infected eye's silicone oil or when inflammation is controlled.

Pearl 6: We recommend the reduced antibiotic dosage (25%) for retreatment in all vitrectomized eyes.

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**Table 4.**

*Pars Plana vitrectomy technique [265].*

1. Perform a core pars plana vitrectomy
2. Perform endolaser around the desired biopsy site
3. Use 23-gauge vertical cutting intraocular scissors to incise the retinal specimen within the laser barrier to close the retinal vessels.
4. Hemostasis is achieved by raising the IOP by lifting the infusion fluid bottle, the vitrectomy instrument is used to slowly aspirate the retinal biopsy which is then removed from the aspiration tube slowly for culture and then proceed to close the sclerotomy.
5. Inject 20% or less sulfur hexafluoride gas/air into the eye.
6. Close the sclera and conjunctiva appropriately with suture if needed.

Pearl 1: Ensure that infusion bottle is raised during biopsy procedure to reduce the risk of intraocular hemorrhage. The infusion can then be turned off once hemostasis is achieved.

Pearl 2: Place the tissue specimen in the culture or fixation solution of choice and then promptly send it for microbiology and histology.

Pearl 3: Minimize any trauma to the biopsy during the procedure and transport.

Pearl 4: Often no further laser treatment or cryotherapy is required at the biopsy site.

Pearl 5: Instruct the patient to lay on the appropriate side to tamponade the site with gas during sleep.

Pearl 6: Closely follow up patients for any signs of retinal detachment.

**Table 5.**  
*Chorioretinal biopsy technique.*

Infusion Fluid Upper limit of drug dosages without toxicity in non-vitrectomized eyes*	
Drug	Nontoxic Dose ( $\mu\text{g/ml}$ )
Single Drugs	
Amikacin	10
Amphotericin B methyl ester	75
Ceftazidime	40
Chloramphenicol	10
Clindamycin	9
Fluconazole	200
Gentamicin	8
Imipenem	16
Lincomycin	10
Methicillin	20
Netilmicin	4
Oxacillin	10
Penicillin	80
Teicoplanin	8
Tobramycin	10
Vancomycin	20
Dexamethasone	64
Combination Drugs	
Clindamycin/Gentamicin	9 / 8

Infusion Fluid Upper limit of drug dosages without toxicity in non-vitreotomized eyes*	
Drug	Nontoxic Dose (µg/ml)
Gentamicin/Oxacillin	8 / 10
Methicillin/Gentamicin	20 / 8
Penicillin/Gentamicin	80 / 8

\*In vitrectomized eyes, one-quarter of the above doses should be used.

**Table 6.**  
Antibiotics in the infusion fluid for pars Plana vitrectomy.

Causative agents of endogenous endophthalmitis discussed in this chapter
Gram-Positive Bacteria
<i>Staphylococcus aureus</i>
<i>Streptococcus pneumoniae</i>
Group B Streptococcus and other Streptococcus species
<i>Listeria monocytogenes</i>
<i>Enterococcus faecalis</i>
Nocardia species
<i>Bacillus cereus</i>
Gram-Negative Bacteria
<i>Klebsiella pneumoniae</i>
<i>Pseudomonas aeruginosa</i>
Neisseria meningitidis
<i>Escherichia coli</i>
Salmonella species
Serratia marcescens
Viruses
Cytomegalovirus
Ebola virus
Epstein-Barr virus
Herpes Simplex virus
SARS-CoV-2
Varicella-zoster virus
Zika virus
Protozoa
Toxoplasmosis gondii
Spirochetes
Borrelia burgdorferi
Leptospira
Treponema pallidum
Mycobacterium
<i>Mycobacterium tuberculosis</i>

<i>Mycobacterium avium</i>
<i>Mycobacterium kansasii</i>
<i>Mycobacterium triplex</i>
<i>Mycobacterium haemophilum</i>
<i>Mycobacterium chelonae</i>
<i>Mycobacterium bovis</i>

**Table 7.**  
*Causative agents of endogenous endophthalmitis discussed in this chapter.*

Clinical presentations may be bilateral or unilateral. Vitreous and retinal involvement are potentially sight threatening and appropriate investigations should be performed to find the distal infection focus or systemic source(s) of the endogenous endophthalmitis and treatment usually involves systemic agents aimed at the offending organism as well as intravitreal pharmacotherapy and/or pars plana vitrectomy (PPV) to both obtain a microbiological sample both to identify the organism and to therapeutically debride the vitreous cavity of the organism, inflammatory cells, and destructive cytokines. Occasionally a chorioretinal biopsy may be required to identify the organism. Despite aggressive treatment, the eye (s) may lose vision, and some may require enucleation.

Addendum Treatment (**Tables 1–7**) [281].

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