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REVIEW ARTICLE

# Antimicrobial guide to posterior segment infections

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## Abstract

**Purpose** This review article is meant to serve as a reference guide and to assist the treating physician in making an appropriate selection and duration of an antimicrobial agent.

**Methods** Literature review.

**Results** Infections of the posterior segment require prompt medical or surgical therapy to reduce the risk of permanent vision loss. While numerous options exist to treat these infections, doses and alternative therapies, especially with contraindications for first-line therapy, are often elusive. Antimicrobial agents to treat posterior segment infections can be administered via various routes, including topical, intravitreal, intravenous, and oral.

**Conclusions** Although there are many excellent review articles on the management of endophthalmitis, we take the opportunity in this review to comprehensively summarize the appropriate antimicrobial regimen of both common and rare infectious etiologies of the posterior segment, using evidence from clinical trials and large case series.

**Key messages**

- Early diagnosis and prompt antimicrobial therapy is essential for treating vision-threatening infections of the posterior segment
- Intravitreal injection of antimicrobial agents is the mainstay of therapy for a majority of infections and is supplemented with systemic therapy taking into account intraocular penetration of systemic antimicrobial agents
- The first-line and alternative therapies for common and rare infections of the posterior segment are summarized and concisely tabulated in this review article.

**Keywords** Antimicrobial · Antiviral · Antihelminthic · Choroiditis · Endophthalmitis · Infectious vitritis · Intravitreal penetration · Posterior segment · Retina · Retinitis

## Introduction

Infections of the vitreous, retina, or choroid (the posterior segment) require prompt treatment in order to reduce the risk of permanent vision loss. Often, the inciting organism is unknown and empiric broad-spectrum therapy is employed until a definitive microbial agent and antimicrobial susceptibilities can be determined. A prime example is endophthalmitis, where prompt broad-spectrum intravitreal antimicrobial therapy administration is imperative until the causative agent can be identified from a diagnostic aqueous or intravitreal fluid sample. Many excellent review articles exist in the literature that discuss

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the epidemiology, clinical presentation, diagnosis, and treatment for various infections of the posterior segment, including bacterial endophthalmitis, fungal endophthalmitis, and viral retinitis. In clinical practice, a single consolidated guide to antimicrobial therapy for infections of the posterior segment can be of benefit to the treating physician. The level of evidence for antimicrobial selection varies considerably, from randomized clinical trial to case series. The purpose of this review article is to summarize the antimicrobial treatment of both the common and rare posterior segment infections. The scope of this article is limited to a discussion of antimicrobial agents, and the reader is referred to other sources for information on clinical presentation and diagnosis. Table 1 summarizes all the antimicrobial agents discussed in this review article. The intravitreal penetration of systemically administered antimicrobial agents (when available) is also listed in Table 1.

## Endophthalmitis

Treatment of endophthalmitis requires intravitreal and/or intravenous systemic antimicrobials depending on the etiology and causative agent. We divide the discussion of endophthalmitis into three major categories: post-surgical, post-traumatic, and endogenous. The antibiotic treatment regimen is summarized in Table 2.

### Post-operative

Discussion of post-operative endophthalmitis is further divided into those infections that arise within 6 weeks of intraocular surgery (acute) and those that arise beyond 6 weeks of surgery (chronic). We also briefly discuss endophthalmitis following intravitreal injection of medications, such as anti-vascular endothelial growth factor (VEGF) agents.

#### Acute post-operative endophthalmitis

Acute endophthalmitis, occurring within 6 weeks after intraocular surgery, can occur if organisms are introduced into the eye as surface fluid refluxes through the wound during surgery or if intraocular hardware (intraocular lens or glaucoma drainage device) is contaminated via contact with the ocular surface. Current practice recommends obtaining ocular samples from all patients with endophthalmitis for microbial identification via a vitreous tap, which has roughly 50 to 70% positive culture rate [39, 40]. If vitreous tap is unsuccessful, an anterior chamber tap can be performed; however, it has a much lower positive culture rate for bacterial endophthalmitis (~ 30%) compared to vitreous tap [41]. The most common isolates in post-surgical endophthalmitis are *Staphylococcus epidermidis* (60–80%), followed by other Gram-positive bacteria—*Staphylococcus aureus*, *Streptococci*, *Enterococci* species, and *Bacillus* species (5–10%)—and Gram-negative species, which include *Proteus*, *Pseudomonas aeruginosa*, *Haemophilus influenza*, and *Klebsiella* (5–10%) [42].

The Endophthalmitis Vitrectomy Study (EVS) [43] is a landmark study in the management of acute post-operative endophthalmitis. Results showed that most post-cataract endophthalmitis can be managed with intravitreal antibiotics only and does not require surgical intervention. However, patients who present with light perception (LP) visual acuity or worse benefit from immediate pars plana vitrectomy (PPV) over intravitreal injection alone. Furthermore, the addition of systemic antibiotics did not affect the final outcome. The intravitreal antibiotics of choice in the EVS include vancomycin and amikacin. Since the EVS, intravitreal empiric antibiotic therapy often includes vancomycin 1.0 mg/0.1 mL PLUS ceftazidime 2.25 mg/0.1 mL. If a patient is allergic to β-lactams, ceftazidime can be replaced with amikacin 400 μg/0.1 mL. However, it is worth noting that approximately 10% of patients report an allergy to penicillin and up to 90% of these patients do not have a true allergy [44]. The cross-reactivity of beta-lactams to third- and fourth-generation cephalosporin is low (less than 5%) and there is no clear evidence of an increased risk of anaphylaxis in ceftazidime-naïve, penicillin-allergic patients [45]. Amikacin, an aminoglycoside, has been reported to cause macular infarction and retinal toxicity [46], whereas intravitreal ceftazidime has a better safety prolife and is equally effective against Gram-negative microbes. EVS reported the sensitivity rate of 89% for both amikacin and ceftazidime and a more recent study showed the sensitivity of Gram-negative bacteria to ceftazidime and amikacin at 99% and 100% respectively in the USA [47].

Reinjection should be considered if the infection fails to stabilize or improve 36–60 h after the first injection. Reinjection interval is guided by the clinical response and is influenced by the half-life of these intravitreal agents. The half-life of intravitreal antibiotics in animal studies are variable: vancomycin (aphakic, 9.0 h; phakic 25.1 h) [48], amikacin (aphakic, 7.4 h; phakic 25.5 h) [49], and ceftazidime (phakic 21.5 h) [50]. Inflammation substantially increases the rate of clearance of intravitreal antibiotics. Given the short half-life of vancomycin and amikacin, it is possible that some sensitive organisms could survive the initial injection, accounting for persistent endophthalmitis and need for a second injection, although this is infrequent.

Antimicrobial agents most effective against the common causative organisms of post-operative endophthalmitis (namely, vancomycin, aminoglycosides, and cephalosporins) have low penetrance in the vitreous cavity when administered intravenously [51]. Although inflammation increases the permeability of the blood-ocular barrier, these antibiotics show highly variable penetrance, often reaching levels below the minimal inhibitory concentration (MIC) for many ocular pathogens. The EVS also evaluated the clinical efficacy of systemic

**Table 1** Common antimicrobials for the treatment of posterior segment infections

| | Drug | Intravitreal dose (per 0.1 mL) | Intravenous | Oral | Topical | Vitreous penetration after systemic administration (intravenous or oral when intravenous formulation unavailable) |
|---|---|---|---|---|---|---|
| Antibacterial | Amikacin | 400 μg | 15 mg/kg/day in 2–3 divided doses | N/A | 10–20 mg/mL | Poor [1, 2] |
| | Ampicillin | 5 mg | 4–12 g/day, in 4 divided doses | N/A | 50 mg/mL | Good [3] |
| | Cefazolin | 2.25 mg | 2–4 g/day in 3–4 divided doses | N/A | 50 mg/mL | Good in inflamed eyes, poor in normal eyes [4] |
| | Cefotaxime | N/A | 2–4 g/day in 3–4 divided doses | N/A | N/A | Poor [5] |
| | Ceftazidime | 2.25 mg | 1 g/day in 2–3 doses | N/A | 50 mg/mL | Poor in normal eyes, good in inflamed aphakic, or vitrectomized eyes [6] |
| | Ceftriaxone | | 1–2 g/day | N/A | N/A | Good [7, 8] |
| | Ciprofloxacin | 100–500 μg* | N/A | 500–700 mg BID | 0.3% | Good [9] |
| | Clarithromycin | | N/A | 500 mg BID | N/A | Good [10] |
| | Clindamycin | 250–1000 μg | 900–1800 mg/day in 2 doses | 300 mg QID | 50 mg/mL | Good [11] |
| | Crystalline penicillin G | N/A | 18–24 million units/day, divided q4h | N/A | N/A | Poor [12] |
| | Daptomycin | 200 μg | 10 mg/kg/day | N/A | N/A | Good [13] |
| | Doxycycline | | | 100–400 mg daily | N/A | Good [14] |
| | Gentamicin | 100–200 μg | 3–5 mg/kg/day in 2–3 doses | N/A | 8–15 mg/mL | Poor [15, 16] |
| | Imipenem | N/A | 2 g/day in 3–4 doses | N/A | 5 mg/mL | Good [17, 18] |
| | Levofloxacin | 625 μg* | 500 mg/day | N/A | 0.5% | Good [19] |
| | Linezolid | 400 μg* | 600 mg BID | 600 mg BID | N/A | Good [19] |
| | Minocycline | N/A | N/A | 100–200 mg BID | N/A | Good [20] |
| | Moxifloxacin | 400 μg* | 400 mg/day | 400 mg daily | 0.50% | Good [21] |
| | Pentamidine | N/A | 4 mg/kg/day | N/A | N/A | Unknown |
| | Probenecid | N/A | N/A | 500 mg QID | N/A | Unknown |
| | Pyrimethamine | N/A | N/A | 25 mg BID | N/A | Unknown |
| | Sulfadiazine | N/A | N/A | 1 g QID | N/A | Unknown |
| | Trimethoprim/sulfamethoxazole | N/A | 160/800 mg q6h | 160/800 mg BID | N/A | Good [22] |
| | Tobramycin | 100-200 μg | 3–5 mg/kg/day in 2–3 doses | N/A | 8–15 mg/mL | Poor [23] |
| | Vancomycin | 1 mg | 15–30 mg/kg/day in 1–2 divided doses | N/A | 20–50 mg/mL | Poor in normal eyes; good in inflamed eyes or normal aphakic or post-vitrectomized eyes [24, 25] |
| Antifungal | Amphotericin B | 5–10 μg | 3–5 mg/kg/day | N/A | 0.15–0.5% | Poor; mild in inflamed eyes [26, 27] |
| | Fluconazole | 10–100 μg* | 800 mg (12 mg/kg/day) | 800 mg (12 mg/kg) daily | 0.2% | Good [28] |
| | Voriconazole | 100 μg | 400 mg (6 mg/kg) BID loading dose; 300 mg (4 mg/kg) maintenance | 200 mg BID | 1–2% | Good [29] |

**Table 1** (continued)

| | Drug | Intravitreal dose (per 0.1 mL) | Intravenous | Oral | Topical | Vitreous penetration after systemic administration (intravenous or oral when intravenous formulation unavailable) |
|---|---|---|---|---|---|---|
| | Flucytosine | N/A | N/A | 25 mg/kg QID | | Good in inflamed eyes [28] |
| | Micafungin | N/A | 150–300 mg/day | N/A | N/A | Moderate [30] |
| | Posaconazole | N/A | N/A | 200 mg QID | 100 mg/mL | Unknown; poor CNS penetration [31, 32] |
| Antiviral | Acyclovir | N/A | 10–15 mg/kg TID | 800 mg 5 times/day | N/A | Good [33] |
| | Valacyclovir | N/A | N/A | 1 g TID | N/A | Good [34] |
| | Famciclovir | N/A | N/A | 500 mg TID | N/A | Good [35] |
| | Foscarnet | 2.4 mg | 60–120 mg/kg BID | N/A | N/A | Moderate [36] |
| | Ganciclovir | 2 mg | 5 mg/kg BID (loading); 5 mg/kg daily (maintenance) | N/A | N/A | Moderate [36] |
| | Valganciclovir | N/A | N/A | 900 mg BID (loading), 900 mg daily (maintenance) | N/A | Moderate [37] |
| | Cidofovir | N/A | 5 mg/kg weekly | N/A | N/A | Unknown |
| Antihelminthic | Albendazole | N/A | N/A | 800 mg BID | N/A | Unknown |
| | Thiabendazole | N/A | N/A | 25 mg/kg BID | N/A | Good [38] |

Scale of vitreous penetration (increasing penetration): poor < mild < moderate < good

*BID*, twice daily; *TID*, three times daily; *QID*, four times daily; *N/A*, unavailable or ineffective formulation for the treatment of posterior segment infections

*Extrapolated from animal studies

**Table 2** Antimicrobial treatment regimen for infectious endophthalmitis

| Category | first-line treatment | Alternative | Duration* |
|---|---|---|---|
| Acute post-operative | • PPV if VA is LP or worse<br>• Intravitreal vancomycin 1 mg/0.1 mL PLUS intravitreal ceftazidime 2.25 mg/0.1 mL<br>If suspect fungal,<br>• Intravitreal amphotericin B 5–10 μg/0.1 mL OR intravitreal voriconazole 100 μg/0.1 mL<br>Consider adjuvant oral moxifloxacin 400 mg daily or levofloxacin 500 mg daily, in addition to intravitreal injection | If PCN allergy:<br>• Replace ceftazidime with intravitreal amikacin 0.4 mg/0.1 mL<br>VRE or VRSA:<br>• Intravitreal ampicillin 5 mg/0.1 mL PLUS intravitreal amikacin 0.25 mg/0.1 mL PLUS intravenous linezolid 600 mg BID | Repeat intravitreal injection 48–72 h later if needed;<br>Oral moxifloxacin therapy for 7–10 days |
| Chronic post-operative | • Intravitreal vancomycin 1 mg/0.1 mL PLUS intravitreal amphotericin B 5–10 μg/0.1 mL or voriconazole 100 μg/0.1 mL if suspect fungal<br>If suspect *P. acnes*,<br>• PPV, total capsulectomy, IOL exchange, and intravitreal vancomycin 1 mg/0.1 mL<br>Filtering bleb-associated endophthalmitis:<br>• Intravitreal vancomycin 1 mg/0.1 mL PLUS intravitreal ceftazidime 2.25 mg/0.1 mL<br>• Topical fortified vancomycin 25 mg/mL and amikacin 20 mg/mL every hour<br>Consider adjuvant oral moxifloxacin 400 mg daily or levofloxacin 500 mg daily, in addition to intravitreal injection | As listed for acute post-operative | Repeat intravitreal injection 48–72 h later if needed.<br>Oral antibiotic therapy for 7–10 days |
| Post-traumatic | • Intravitreal vancomycin 1 mg/0.1 mL and intravitreal ceftazidime 2.25 mg/0.1 mL PLUS<br>• Intravenous vancomycin or levofloxacin 500 mg daily for 3–5 days, followed by oral moxifloxacin 400 mg daily<br>If suspect *Bacillus*,<br>• Intravitreal vancomycin 1 mg/0.1 mL PLUS intravenous vancomycin PLUS topical fortified vancomycin 25 mg/mL and topical fortified tobramycin 14 mg/mL every hour<br>If suspect *Clostridium*,<br>• Intravitreal vancomycin 1 mg/0.1 mL PLUS intravitreal ceftazidime 2.25 mg/0.1 mL PLUS intravitreal clindamycin 1 mg/0.1 mL<br>• Intravenous vancomycin AND either clindamycin or metronidazole | For severe infection, consider the addition of<br>• Intravitreal clindamycin 250 μg/0.1 mL, intravitreal ciprofloxacin 100 mg/0.1 mL or amikacin | Systemic antibiotic for 3–5 days, followed by oral therapy for 7–10 days |
| Endogenous bacterial | • Intravitreal vancomycin 1 mg/0.1 mL and intravitreal ceftazidime 2.25 mg/0.1 mL PLUS<br>• Intravenous vancomycin and cefepime 2 g TID<br>If VRSA:<br>• Intravitreal daptomycin 200 μg/0.1 mL PLUS<br>• Intravenous daptomycin 10 mg/kg<br>If VRE:<br>• Intravitreal amikacin 400 μg/0.1 mL PLUS<br>• Oral linezolid 600 mg BID | If severe PCN and cephalosporin allergy, replace intravenous cefepime with intravenous levofloxacin 750 mg daily | Systemic antibiotic therapy for 10–14 days after source control and negative blood cultures |

**Table 2** (continued)

| Category | first-line treatment | Alternative | Duration* |
|---|---|---|---|
| Nontuberculous mycobacterium | Intravitreal amikacin 0.4 mg/0.1 mL PLUS topical fortified amikacin 2.5% PLUS clarithromycin 500 mg oral BID | Often requires explant of infected hardware. | Systemic antibiotic therapy for 1–2 months |
| Nocardia endophthalmitis | • Trimethoprim-sulfamethoxazole (TMP/SMX) 160/800 mg intravenous QID or two double-strength pills BID PLUS intravitreal amikacin 400 μg/0.1 mL | Oral TMP-SMX double-strength BID PLUS either of the following:<br>– Intravenous ertapenem 1 g daily and intravitreal amikacin 200 μg/0.1 mL weekly for 7 weeks<br>– Intravitreal amikacin 200–400 μg/0.1 mL<br>– Intravenous ceftriaxone 2 g daily and amikacin 15 mg/kg/day, and intravitreal amikacin 400 μg/0.1 mL<br>– Intravitreal amikacin 400 μg/0.1 mL) and cefazolin 2.25 mg/0.1 mL | Systemic antibiotic therapy for 3–6 weeks |
| Fungal: *Candida* | If there is only chorioretinitis without vitritis:<br>• Intravenous/oral fluconazole 800 mg BID OR<br>• Intravenous voriconazole 400 mg (6 mg//kg BID for 1 day) then 300 mg (4 mg/kg) BID<br>OR<br>• Intravenous micafungin 100 mg/day<br>*Confirmed or suspected cases of *Candida glabrata* and *Candida krusei* are resistant to fluconazole and should be treated with voriconazole.<br>If there is vitritis or chorioretinitis near the macula or optic nerve, in addition to above:<br>• Intravitreal voriconazole 100 μg/0.1 mL OR amphotericin B 5 μg/0.1 mL | For fluconazole or voriconazole-resistant isolates<br>• Intravenous liposomal amphotericin B 3–5 mg/kg daily PLUS oral flucytosine 25 mg/kg QID<br>Posaconazole, echinocandins, micafungin, capsofungin, and anidulafungin are not recommended if there is vitritis due to poor intravitreal penetration. | Systemic antifungal therapy is 4–6 weeks, possibly longer depending on the resolution of chorioretinal lesions on serial funduscopic examinations. |
| Fungal: *Aspergillus* | • Consider early PPV if dense vitritis.<br>• Intravitreal voriconazole 100 μg/0.1 mL OR amphotericin B 5 μg/0.1 mL<br>PLUS<br>• Intravenous voriconazole 6 mg/kg BID for 2 doses, then 3–4 mg/kg BID oral/intravenous | Consider intravenous liposomal amphotericin B or intravenous anidulafungin for voriconazole-resistant isolates | Systemic antifungal therapy for 3–4 weeks |
| Fungal: *Fusarium* | • Intravitreal voriconazole 100 μg/0.1 mL PLUS Intravenous voriconazole 6 mg/kg BID for 2 doses, then 3–4 mg/kg BID oral/intravenous | If concern for hepatotoxicity with voriconazole:<br>• Substitute voriconazole with oral posaconazole 200 mg QID PLUS topical posaconazole 100 mg/mL every hour | Systemic antifungal therapy for 4–6 weeks |
| Other fungal endophthalmitis: coccidiomycosis, cryptococcosis, blastomycosis, histoplasmosis | • Intravitreal and intravenous voriconazole or amphotericin B PLUS<br>• Oral fluconazole 800 mg daily for an extended period | N/A | Initial intravenous treatment with voriconazole or amphotericin B for 1–2 weeks, then prolonged treatment with oral fluconazole for 4–6 weeks (longer if immunosuppressed) |

*PCN*, penicillin; *PPV*, pars plana vitrectomy; *N/A*, not applicable; *BID*, twice daily; *TID*, three times daily; *QID*, four times daily; *VA*, visual acuity; *LP*, light perception; *VRE*, vancomycin-resistant *Enterococcus*; *VRSA*, vancomycin-resistant *Staphylococcus aureus*; *IOL*, intraocular lens

*Duration of therapy is only a starting guide and should be adjusted based on the clinical course

antibiotics plus intravitreal injection versus intravitreal injection alone and found no clear benefit of adjuvant systemic antibiotics. However, the intravenous antibiotics used in the EVS were not optimal choices for complementary therapy to intravitreal antibiotics since amikacin does not penetrate well into the vitreous cavity and ciprofloxacin does not adequately treat *S. aureus* and *S. epidermidis*. At the time of the EVS study, oral fourth-generation fluoroquinolones, such as moxifloxacin, were not available. Given the excellent intraocular penetration of oral moxifloxacin [52] and activity against many Gram-positive and Gram-negative pathogens implicated in post-operative endophthalmitis, it may provide benefit as an adjunct to intravitreal antibiotics. However, there is no clinical trial investigating the role of adjuvant oral moxifloxacin for the treatment of acute post-operative endophthalmitis and controversy exists as to whether systemic antibiotics provide benefit in the setting of intravitreal antibiotic injection. Of note, oral moxifloxacin does not achieve vitreous $MIC_{90}$ levels for *Pseudomonas aeruginosa* and *Bacteroides fragilis*. In a study by Hooper et al., patients with acute bacterial post-operative endophthalmitis treated with adjuvant moxifloxacin (in addition to intravitreal vancomycin and amikacin) had faster resolution of hypopyon and reduced need for repeat intravitreal injections; however, visual acuity outcomes were unchanged [53]. The typical dose and duration of oral moxifloxacin are 400 mg daily for 7 to 10 days. In patients who do not have access to oral moxifloxacin, a third-generation fluoroquinolone, such as oral levofloxacin 500 mg daily for 7 to 10 days is a good alternative. Orally administered levofloxacin has good intravitreal penetration [54, 55] and covers most common causative organisms of bacterial endophthalmitis, with the exception of *Pseudomonas aeruginosa*.

Gram-negative bacteria account for a small fraction of post-operative endophthalmitis. The majority of times, the causative agent of endophthalmitis, is unknown so empiric therapy to cover both Gram-positive and Gram-negative bacteria is initiated. The common Gram-negative organisms causing endophthalmitis are *Pseudomonas*, *Haemophilus*, *Klebsiella*, and *Proteus*, which are typically sensitive to intravitreal ceftazidime or amikacin [56–58]. *Pseudomonas* post-operative endophthalmitis typically occurs in clusters, related to the use of contaminated multidose vials, irrigating solutions, contaminated intraocular lens, or phacoemulsifier [59–61]. Post-operative *Haemophilus* endophthalmitis has been reported following cataract extraction, PPV, trabeculectomy, secondary IOL implantation, and post-suture removal from an extracapsular cataract wound [57]. Both organisms are very virulent and cause a rapid, destructive endophthalmitis that is difficult to treat, despite treatment with intravitreal antibiotics to which the organisms are sensitive [58]. Patients typically present with severely decreased visual acuity (less than 20/400), significant anterior chamber reaction, hypopyon, and corneal edema [62]. Treatment often involves early PPV and intravitreal vancomycin and ceftazidime.

*Klebsiella pneumoniae* is a less commonly encountered cause of acute post-operative endophthalmitis. *Klebsiella* can be difficult to treat because it can carry carbapenemase and ß-lactamase enzymes that make it resistant to most modern antibiotics, leaving limited and suboptimal options for treatment. In one case report, patients with post-operative endophthalmitis caused by multidrug-resistant *Klebsiella pneumoniae* were treated with PPV and intravitreal injection of imipenem 50 μg/0.1 mL, although the visual outcome was either phthisis or blindness, and it is unclear whether intravitreal injection of imipenem eradicated the bacterial infection [63].

### Endophthalmitis after intravitreal injection

Endophthalmitis following intravitreal injection is a concern, especially as intravitreal injection of medications is becoming increasingly common for the treatment of various retinal disorders. Like acute post-operative endophthalmitis, most cases of endophthalmitis secondary to intravitreal injection of medication are due to coagulase-negative *Staphylococci* and can be managed by acquiring ocular sample for culture and intravitreal injection of vancomycin and ceftazidime ± PPV when inflammation is severe.

### Delayed-onset and chronic post-operative endophthalmitis

Delayed-onset post-operative endophthalmitis occurs greater than 6 weeks after the presumed causative surgery. Chronic post-operative endophthalmitis occurs weeks to months after the presumed causative surgery and consists of recurrent episodes of low-grade inflammation. Delayed-onset and chronic post-operative endophthalmitis is caused by sequestration of low-virulence organisms introduced at the time of the surgery or due to delayed inoculation of organisms (for example, through suture tracks or a filtering bleb). The most common organisms are *Propionibacterium* species (majority of cases), *Staphylococcus epidermidis*, *Candida parapsilosis*, and *Corynbacterium* species [64]. Other reported pathogens include *Actinomyces* [65], *Nocardia* [66], *Achromobacter*, *Cephalosporium*, *Acremonium*, *Paecilomyces*, and *Aspergillus* species.

Pain or discomfort may or may not be present in chronic post-operative endophthalmitis and inflammation can be initially steroid responsive but recurrent after a steroid taper. A white intracapsular plaque is commonly observed with *Propionibacterium* species. Stringy white infiltrates and "fluff-balls" near the capsular remnant are seen in fungal infections. Typically, there is mild vitritis, except in cases of *S. epidermidis*, which causes dense, diffuse vitritis. Although clinical exam gives clues about the causative organism, identification of the infectious organism via aqueous or vitreous sample is key in management. Since delayed-onset and chronic endophthalmitis can often be present for weeks

prior to the patient presenting to the ophthalmologist, it may be reasonable to wait for culture and sensitivity data before initiating therapy, especially if inflammation is not severe. Empiric treatment involves intravitreal vancomycin 1 mg/0.1 mL for bacterial infections and an antifungal agent (amphotericin B 5–10 μg/0.1 mL or voriconazole 100 μg/0.1 mL) for suspected fungal endophthalmitis. Most pathogens implicated in chronic post-operative endophthalmitis are susceptible to vancomycin; however, empiric therapy should include intravitreal ceftazidime or amikacin. Given the indolent course of infection, systemic antibiotic therapy may provide a possible benefit; however, definitive evidence showing improved visual outcomes with adjuvant systemic antibiotic therapy does not exist.

***Propionibacterium acnes* endophthalmitis** *Propionibacterium acnes* deserves further discussion since it is the most common cause of delayed post-cataract surgery endophthalmitis. *P. acnes* is an anaerobic, pleomorphic, Gram-positive bacillus that is present in the normal flora of the eyelid margin and conjunctiva. The hallmark of *P. acnes* infection is the presence of a white plaque on the posterior capsule or intraocular lens (IOL), which may be the site of sequestration of the bacterium [67, 68]. As the disease is relatively uncommon, reported cases and series have involved small numbers of patients. Injection of intravitreal vancomycin 1 mg/0.1 mL alone is associated with a high rate of recurrence, likely because the organism remains sequestered in the posterior capsule or on the IOL [69]. The preferred strategy for treatment, with a low rate of recurrence, is PPV and intravitreal vancomycin 1 mg/0.1 mL with total capsulectomy and IOL exchange or removal [69, 70]. Occasionally, the infection and ensuing inflammation can be controlled with repeat intravitreal vancomycin injections, especially in patients unable to undergo surgical intervention.

**Fungal endophthalmitis** Fungal endophthalmitis following intraocular surgery is very rare, usually a result of contaminated laboratory solution [71, 72] and harbors a poor prognosis. It typically presents with poor visual acuity (20/200 or worse), significant anterior chamber reaction with hypopyon and fluffy fibrin coating the IOL surface, and fluffy vitreous exudates. Aggressive treatment with both intravitreal and systemic antifungal agents, as described below (Fungal endophthalmitis), is recommended.

**Atypical mycobacterial endophthalmitis** Atypical mycobacteria or nontuberculous mycobacteria are aerobic, non-motile, acid-fast bacilli that are widespread in the environment and can be the cause of chronic endophthalmitis, especially in an immunocompromised host. The most common nontuberculous mycobacterium species isolated from patients with endophthalmitis are *Mycobacterium fortuitum* and *M. chelonae*. Management strategies for nontuberculous mycobacteria are not well defined; as such, we provide evidence from case series of attempted therapies in the following discussion.

Shah et al. [73] report a case series of 19 patients with atypical mycobacterial endophthalmitis. The majority of isolates were susceptible to amikacin and clarithromycin. The proposed treatment regimen includes the removal of intraocular hardware (intraocular lens or glaucoma drainage device), PPV, intravitreal injection of amikacin 0.4 mg/0.1 mL and vancomycin 1 mg/0.1 mL, and systemic antibiotics (oral clarithromycin, azithromycin, or ciprofloxacin) [73]. Another case series by Hsu et al. [74] report 9 cases of endophthalmitis after cataract surgery caused by nontuberculous mycobacterium. These patients were treated in a similar manner with PPV, removal of the intraocular lens, intravitreal amikacin, and vancomycin. Systemic antibiotics including amikacin and tigecycline were prescribed for 10 days and clarithromycin for 3 months. In both these series, despite adequate treatment, the visual outcome was poor.

**Filtering bleb-associated endophthalmitis** Filtering bleb-associated endophthalmitis (BAE) can occur in the early post-operative period, but more often occurs months to years after surgery, with a mean time between glaucoma filtering surgery and endophthalmitis of 19.1 months (range 3 days to 9 years) [75]. Endophthalmitis in the acute post-operative period may be treated according to the EVS recommendations. But, it is more likely that patients with BAE typically have a delayed presentation (> 6 weeks from surgery) of endophthalmitis and with more virulent organisms (predominantly *Streptococcus* species and a larger proportion of Gram-negative organisms). It is unclear if the conclusions of EVS can be generalized to BAE. Busbee et al. [75] performed a retrospective case review of 68 patients with BAE treated in the pre-EVS and post-EVS era and found a significantly higher percentage of patients treated with tap/inject (vancomycin and ceftazidime) in the post-EVS years (51% vs 14%). In this cohort of 68 patients, patients appeared to benefit from early PPV compared with tap/inject with a greater likelihood of attaining 20/100 vision. However, a separate series by Song et al. [76] reported on 49 patients with BAE and found 69% of patients treated with tap/inject had final visual acuity greater than 20/400, compared to 36% treated with early PPV. Successful management of BAE remains elusive. Considering that more virulent bacteria typically cause BAE, it is plausible that early PPV helps decrease the bacterial load within the infected eye and may help preserve retinal function. BAE may also benefit from the addition of topical fortified antibiotics such as vancomycin 25 mg/mL and amikacin 20 mg/mL alternating every hour. In addition, systemic therapy with oral moxifloxacin 400 mg daily for 7 to 10 days may have a role in the treatment of BAE; however, given the

relatively infrequent occurrence of BAE, good-quality evidence for use of adjuvant oral moxifloxacin does not exist. Removal of a glaucoma drainage device is controversial and successful outcomes may be achieved without having to remove the implant [77].

## Post-traumatic

Post-traumatic endophthalmitis requires prompt intravitreal antibiotic and often systemic antibiotic therapy. The incidence of endophthalmitis following open-globe trauma ranges from 3.1 to 11.9% in the absence of an intraocular foreign body (IOFB), and higher rates are noted in eyes with an IOFB contaminated with organic matter [78]. The main causative bacterial agents found in post-traumatic endophthalmitis patients are *Staphylococci*, *Streptococci*, and Gram-positive and Gram-negative bacilli [79].

### Bacterial endophthalmitis

Among Gram-positive microbes, *Staphylococcus epidermis* is the most commonly isolated organism. It is part of the normal skin flora and likely gains access to the eye through the eyelid or eyelashes in an open-globe injury. *Staphylococcus aureus* less commonly is isolated in post-traumatic endophthalmitis. It gains access to the eye through a breach in the skin or mucosa. Empiric treatment for suspected post-traumatic endophthalmitis is tailored against Gram-positive and Gram-negative organisms and includes intravitreal vancomycin and ceftazidime injections. In addition, systemic intravenous vancomycin or a third-generation fluoroquinolone (e.g., levofloxacin 500 mg daily) for 3 to 5 days, followed by oral fluoroquinolone (e.g., moxifloxacin 400 mg daily) therapy, is recommended [80].

Soil-contaminated intraocular foreign bodies carry a risk of infection with *Bacillus* and *Clostridium* species. *Bacillus* species are Gram-positive, spore-forming rods. *Bacillus cereus*, in particular, causes one of the most explosive and devastating endophthalmitis infections with a severe intraocular inflammatory response and often very poor visual outcomes. Endophthalmitis caused by *Bacillus* species can cause rapid complete corneal opacification; severe pain develops within 24 h and deterioration of vision within 48 h of trauma. *Bacillus* species are usually resistant to most penicillins and cephalosporins but are usually sensitive to vancomycin. Empiric treatment consists of intravitreal vancomycin and intravenous vancomycin with topical fortified vancomycin and tobramycin alternating every hour. For severe cases, intravitreal clindamycin 250 μg/0.1 mL, intravitreal ciprofloxacin 100 mg/0.1 mL, or intravitreal amikacin can be added to the regimen [81, 82].

Similar to *B cereus*, *Clostridium perfringens* endophthalmitis carries a very poor visual prognosis and many cases require enucleation. It is usually encountered in the setting of a contaminated penetrating intraocular foreign body. Removal of foreign body and early vitrectomy may aid in the reduction of the bacterial load and offer a better chance of retaining the eye and vision. *Clostridium* species are generally susceptible to vancomycin, but given its virulence, double coverage with vancomycin and clindamycin is necessary. Presumed clostridial endophthalmitis should be treated with a combination of intravitreal vancomycin, ceftazidime, and clindamycin (1 mg/0.1 mL) injections. In addition, systemic treatment with intravenous vancomycin and either clindamycin or metronidazole for 10 to 14 days is also recommended [83, 84].

### Fungal endophthalmitis

Post-traumatic fungal endophthalmitis is less common than bacterial, with an incidence ranging from 0 to 15.6%. The most common organism is *Candida albicans*, followed by *Fusarium* and *Aspergillus*. The risk of fungal post-traumatic endophthalmitis is increased if the injury is caused by an object containing vegetative matter. Fungal endophthalmitis typically presents 1 to 5 weeks after the initial injury with slowly progressive intraocular inflammation, and a "fluffy ball" of vitreous or anterior chamber opacity. The external eye exam is typically benign and the patient may have minimal discomfort. Empiric treatment for suspected fungal endophthalmitis consists of intravitreal amphotericin B (5–10 μg/0.1 mL) or intravitreal voriconazole 50 μg/0.1 mL PLUS systemic antifungal therapy [80]. Voriconazole has excellent in vitro susceptibility to *Candida*, *Fusarium*, and *Aspergillus* and is the drug of choice for empiric systemic therapy. The typical dose for intravenous or oral voriconazole is 400 mg BID for the first 24 h (loading dose), followed by 200 mg BID for 7–10 days.

### Role of vitrectomy

The role of vitrectomy with intravitreal antibiotic injection versus intravitreal injection alone is uncertain. Early vitrectomy offers many perceived benefits, such as removal of infectious inoculum, elimination of vitreous scaffolding that exert traction on the retina, and clearing of the media for serial fundus exams. Retrospective studies suggest that vitrectomy with intravitreal antibiotics may not be superior to intravitreal injection alone, but these studies are likely biased because only those eyes with more severe inflammation underwent early vitrectomy, whereas less severe endophthalmitis was treated with intravitreal injections alone. In the absence of a randomized clinical trial, there is no clear consensus. However, in the case of post-traumatic endophthalmitis with an IOFB or fungal endophthalmitis, prompt vitrectomy is recommended [85].

## Endogenous endophthalmitis

Endogenous endophthalmitis is typically encountered in sick hospitalized patients. It almost always requires a combination of intravitreal and systemic antimicrobial therapy. We divide the discussion of endogenous endophthalmitis into two broad categories: bacterial and fungal.

### Bacterial endophthalmitis

Bacterial endogenous endophthalmitis requires systemic antibiotic therapy and source control to eradicate bacteremia. Intravitreal antibiotics can be instituted to achieve a rapid and high intraocular concentration of antimicrobial agents. In severe cases, PPV may also be needed. When the etiology of endophthalmitis is unknown, treatment is first initiated with empirical broad-spectrum intravitreal antibiotics that provide coverage for both Gram-positive and Gram-negative organisms. These include vancomycin 1 mg/0.1 ml plus either ceftazidime 2.25 mg/0.1 mL or amikacin 0.4 mg/0.1 mL (for patients with ß-lactam allergy).

For Gram-positive infections, both intravenous and intravitreal vancomycin is the drug of choice. We highlight several special scenarios when an alternative regimen is needed, either due to vancomycin-resistant strains or atypical bacterial endophthalmitis.

**Vancomycin-resistant *Staphylococcus* and *Enterococcus*** Vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE) endogenous endophthalmitis are frequently encountered in sick, hospitalized patients. Quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline all have activity against VRSA and these agents have been used to treat bacteremia caused by vancomycin-resistant bacteria. However, there is a paucity of evidence on the best agent for the treatment of VRSA endophthalmitis. Several early case reports present successful treatment of VRSA endophthalmitis by the administration of intravitreal quinupristin/dalfopristin 0.4 mg/0.1 mL [86]. Newer agents however have replaced quinupristin/dalfopristin in clinical practice. Daptomycin in particular demonstrates good in vitro bactericidal activity for various vancomycin-resistant strains of bacteria, including *S. epidermidis*, *S. aureus*, *S. pneumoniae*, *E. faecalis*, and *E. faecium*. Daptomycin shows good safety when administered intravitreally at a dose of 200 μg/0.1 mL [87] and has sufficient intraocular penetration when intravenously administered at a standard dose 10 mg/kg [13]. In addition, daptomycin has also been reported to successfully treat VRSA endophthalmitis [88]. Thus, most cases of VRSA endophthalmitis are treated with intravitreal and intravenous daptomycin [89]. Duration of systemic treatment is usually for 10 to14 days after negative blood cultures. Although tigecycline also has good in vitro activity against VRSA, intravenously administered doses do not achieve sufficient vitreous concentration and likely have limited or no role in the treatment of endophthalmitis [90].

Vancomycin-resistant *Enterococcus* (VRE) is often sensitive to linezolid and gentamicin. Intravitreal gentamicin carries dose-dependent retinal toxicity, while the safety of intravitreal linezolid in humans is unknown. Fortunately, oral linezolid 600 mg BID has good intraocular penetration [19]. Systemic oral linezolid and intravitreal amikacin have been reported to successfully treat VRE endophthalmitis [91, 92].

***Klebsiella pneumonia* endophthalmitis** Endogenous *Klebsiella pneumonia* endophthalmitis is a disastrous infection, often occurring in patients with pyogenic liver abscesses [93–95]. It is more common in patients with underlying diabetes and is seen more frequently in East Asia. Attempts to treat *Klebsiella* endophthalmitis with intravitreal injections of vancomycin and ceftazidime and intravenous ceftriaxone often result in poor visual outcomes [95]. More recently, Liu et al. [96] report a case of endogenous *K. pneumoniae* endophthalmitis treated with both intravenous ceftriaxone and oral levofloxacin 500 mg BID. They argue that although intravenous ceftriaxone may be an adequate treatment for liver abscess, it may not achieve a high enough intraocular concentration to be effective against *Klebsiella* endophthalmitis. However, orally administered levofloxacin achieves good intravitreal penetration (average concentration of 2.8 ± 0.8 μg/mL) that is well above the $MIC_{90}$ of *Klebsiella pneumoniae* (0.13 μg/mL).

***Nocardia* endophthalmitis** *Nocardia* species are Gram-positive branching filamentous bacteria with hyphae that share similarities with fungi. *Nocardia asteroides* accounts for the majority of human infections. It is found in soil and decaying vegetative matter and known to cause chorioretinitis and subretinal/choroidal abscess in a small number of solid organ transplant recipients [97, 98]. Systemic infection usually occurs in immunocompromised patients and can involve abscess formations in the lungs, brain, skin, and eyes. Diagnosis is made via blood culture, transvitreal fine-needle aspiration biopsy of the subretinal abscess or biopsy of any affected sites.

Treatment consists of a reduction or discontinuation of immunosuppressives and prolonged combination of systemic antibiotic therapy with or without intravitreal injections. Most *Nocardia* species are susceptible to sulfonamides. The preferred regimen is intravenous trimethoprim-sulfamethoxazole (TMP-SMX) 160 mg/800 mg QID or two pills of the double-strength tablet BID. Although TMP-SMX is the treatment of choice, combination therapy with multiple agents may be more effective, as discussed below. Patients generally require long-term maintenance antibiotic therapy with TMP-SMX (often up to a year) [99, 100]. Adverse

reactions to high-dose TMP-SMX therapy are frequent and include myelosuppression, hepatotoxicity, and renal insufficiency.

Alternative antimicrobial agents with activity against *Nocardia* include amikacin, imipenem, meropenem, ceftriaxone, cefotaxime, minocycline, moxifloxacin, levofloxacin, linezolid, tigecycline, and amoxicillin-clavulanic acid. Of the fluoroquinolones, moxifloxacin is fairly active in vitro against *N. asteroides* complex. Linezolid is quite active against virtually all known pathogenic *Nocardia* species and has successfully been used in the treatment of patients with disseminated and central nervous system (CNS) nocardiosis. Problems with linezolid, however, include its high cost and significant toxicities, including myelosuppression, peripheral neuropathy, and lactic acidosis.

In patients with a sulfonamide allergy or found to have sulfonamide-resistant organisms, therapy should be started with amikacin plus one of the following: imipenem, ceftriaxone, or cefotaxime. Treatment with intravenous agents should be continued for 3 to 6 weeks and then switched to oral if there is clinical improvement. Minocycline 400 mg oral daily is a good oral alternative to sulfonamides in patients with an allergy.

In patients with *N. farcinica*, which has variable sensitivity to sulfamethoxazole, combination therapy, with one of the regimens listed in Table 2, may be especially important [101–103].

### Fungal endophthalmitis

Fungal endophthalmitis is usually a result of *Candida* species; however, less commonly, *Fusarium* or *Aspergillus* may cause endogenous endophthalmitis.

***Candida* endophthalmitis** Most cases of fungemia are due to *Candida* species. *Candida albicans*, *Candida dubliniensis*, *Candida parapsilosis*, *Candida tropicalis*, *Candida lusitaniae*, *Candida krusei*, and *Candida glabrata* have all been reported to cause endogenous endophthalmitis. According to the Infectious Disease Society of America (IDSA) guidelines [104], *Candida* chorioretinitis without vitritis can be treated with systemic antifungal agents alone without intravitreal injection. Two common regimens are:

- fluconazole 800 mg daily (12 mg/kg) intravenous/oral
- voriconazole, loading dose 400 mg (6 mg/kg) intravenous BID for two doses, then 300 mg (4 mg/kg) intravenous/oral BID

Although voriconazole in vitro has a better pharmacokinetic profile than fluconazole, both agents achieve sufficient intraocular penetration. For fluconazole/voriconazole-susceptible isolates, fluconazole may be preferred as it is once a day dosing, has equivalent bioavailability in oral or intravenous form, does not require therapeutic drug level monitoring, and is less hepatotoxic [105]. Micafungin is also an acceptable, albeit less frequently utilized, alternative antifugal agent for the treatment of *Candida* or *Aspergillus* chorioretinitis. At a typical dose of intravenous 100 mg/day, micafungin has good retinal and choroidal bioavailability, but it has poor vitreous penetration and therefore should only be used in cases of candidemia without vitritis [106]. An advantage of micafungin over fluconazole is its sensitivity against *Candida glabrata* species and *Aspergillus*.

For fluconazole/voriconazole-resistant isolates, intravenous liposomal amphotericin B 3–5 mg/kg daily with oral flucytosine 25 mg/kg QID is recommended. Amphotericin B has poor intraocular penetration, but flucytosine has good vitreal penetration in inflamed eyes so combination therapy is beneficial (especially if there is vitritis) to ensure the adequate concentration of antifungal agents. If there is macular involvement, without definite vitritis, intravitreal injection of amphotericin B 5–10 μg/0.1 mL or voriconazole 100 μg/0.1 mL is recommended to ensure a rapid high level of antifungal activity to the retina [107].

*Candida glabrata* and *Candida krusei* isolates are usually resistant to fluconazole and should be treated with voriconazole 6 mg/kg oral/intravenous BID loading dose (2 doses), followed by 3–4 mg/kg oral/intravenous BID. The total duration of therapy for any *Candida* endophthalmitis is usually 4 to 6 weeks, depending on the resolution of chorioretinal lesions based on serial fundoscopic examination.

If, in addition to chorioretinitis, there is also vitritis, intravitreal antifungal (amphotericin B or voriconazole) is recommended, in addition to the systemic therapy as described above. In deciding between intravitreal amphotericin B or voriconazole, the authors prefer amphotericin B since it has a prolonged half-life of 8.9 days [108] in the vitreous, compared to a half-life of 2.5 to 6.5 h of voriconazole [109]. Although systemically administered amphotericin B carries many side effects and is generally reserved to treat severely ill patients, intravitreal amphotericin B is very well tolerated and has not been reported to cause systemic side effects.

Of note, echinocandins, micafungin, capsofungin, and anidulafungin are not recommended for the treatment of fungal endophthalmitis due to their poor vitreous penetration [30, 110].

***Aspergillus* endophthalmitis** *Aspergillus* endophthalmitis is difficult to treat because it often involves the macula. *Aspergillus* endophthalmitis occurs in patients with disseminated aspergillosis with either severe chronic pulmonary disease, cancer, endocarditis, and intravenous drug abuse or recipients of orthotopic liver transplant [111]. Disseminated *Aspergillus* most commonly involves the lung with the eye being the second most commonly involved site. *Aspergillus*

*fumigatus* and *A. flavus* are the two most frequently isolated species from patients with endophthalmitis. In the eye, it causes a confluent yellow infiltrate, often in the macula, in the choroid and subretinal space, with retinal hemorrhages, vascular occlusion, and necrosis [112]. Diagnosis is made based on clinical findings and positive results from vitreous biopsy and cultures. Given its potential for dense vitritis and retinal necrosis, aggressive treatment with diagnostic and therapeutic PPV combined with intravitreal and intravenous voriconazole or amphotericin B is required [113]. However, even if the ocular infection is cleared, the final visual outcome is poor if there is macular involvement, as is often the case. Voriconazole is the first-line agent for the treatment of invasive aspergillosis. Voriconzole-resistant isolates can be treated with intravenous amphotericin B or intravenous anidulafungin 100–200 mg/day; however, vitreal penetration of anidulafungin is poor [114]. Serum levels of voriconazole should be monitored, with goal trough level between 2 and 5 μg/mL.

Both *Candida* and *Aspergillus* endophthalmitis have similar clinical findings with fluffy chorioretinal infiltrates and vitritis. Given voriconazole's activity against most *Candida* and *Aspergillus* species, we recommend empiric treatment with intravitreal and intravenous voriconazole in suspected fungal endophthalmitis. If, however, candidemia is confirmed, fluconazole may be a better systemic option since it has great intravitreal penetration, has few systemic side effects unlike voriconazole which can be hepatotoxic, and does not require therapeutic drug level monitoring.

***Fusarium* endophthalmitis** *Fusarium* species very rarely causes endophthalmitis. *Fusarium* typically causes keratitis and is managed with topical medications, but it can infrequently progress to endophthalmitis [115]. In immunocompromised hosts, disseminated fusariosis can cause endogenous endophthalmitis [116, 117]. *Fusarium* species are resistant to many antifungal agents with equivocal in vitro and in vivo susceptibility to amphotericin B. However, voriconazole shows in vitro efficacy against *Fusarium* and many case reports have shown the efficacy of voriconazole in the treatment of fusariosis [118]. Few case reports demonstrate successful treatment of *Fusarium* endophthalmitis with oral posaconazole 200 mg QID plus topical posaconazole 100 mg/mL and vitrectomy [119, 120]. However, the intravitreal concentration of posaconazole at the time of vitrectomy was below the $MIC_{50}$ and it is unclear if the success of these case studies can be generalized. One potential use of posaconazole is in the treatment of patients with *Aspergillus* or *Fusarium* that are intolerant of systemic voriconazole due to hepatotoxicity since there is a lack of cross-hepatotoxicity between posaconazole and voriconazole [121]. We recommend initial treatment with intravitreal voriconazole 100 μg/0.1 mL and intravenous voriconazole 6 mg/kg BID on the first day and 4 mg/kg BID thereafter for *Fusarium* endophthalmitis and a subsequent trial of oral posaconazole if there is no improvement. Treatment duration is typically at least 4 to 6 weeks.

***Coccidioides* endophthalmitis** *Coccidioides* species is a dimorphic fungus that is endemic in certain parts of Arizona, California, Nevada, New Mexico, Texas, Utah, and northern Mexico. It is a common cause of acute, benign, self-limiting pulmonary disease. It can occasionally cause disseminated infection with focal infectious granulomatous choroiditis, retinitis, and endophthalmitis [122, 123]. Treatment of endogenous coccidioidal endophthalmitis is with intravenous voriconazole (6 mg/kg BID loading dose and then 4 mg/kg BID for 1 to 2 weeks) and intravitreal voriconazole followed by prolonged oral fluconazole 800 mg daily[124] or intravenous amphotericin B and intravitreal amphotericin B [125]. With the advent of voriconazole, intravenous amphotericin B is less widely used given its side effect profile.

***Cryptococcus* endophthalmitis** Cryptococcosis causes a chronic pulmonary infection or meningitis and is caused by *Cryptococcus neoformans*, an encapsulated yeast. Patients with cryptococcal meningitis can have ocular manifestations, including papillitis, papilledema, multifocal choroidal lesions, or subretinal masses. Systemic voriconazole or amphotericin B along with intravitreal voriconazole or amphotericin B has been shown to eliminate the infection successfully [126, 127].

**Blastomyces endophthalmitis** Blastomycosis, caused by *Blastomyces dermatitidis*—a dimorphic fungus—typically causes pulmonary and cutaneous granulomas. Disseminated blastomycosis occurs more frequently in immunosuppressed individuals, such as organ transplant recipients and those infected with HIV. It rarely affects the eye, other than the eyelid. Ocular manifestations include multifocal choroiditis and endophthalmitis [128, 129]. There are no clear guidelines for the treatment of ocular lesions associated with disseminated blastomycosis. It is recommended that intraocular blastomycosis be treated as CNS equivalent [130]. CNS blastomycosis is treated with intravenous liposomal amphotericin B 3–5 mg/kg/day for 4–6 weeks and then oral fluconazole 800 mg/day or oral voriconazole 200–400 mg BID for at least 12 months [130–132]. It is unclear if intravitreal treatment is beneficial.

***Histoplasma* endophthalmitis** Histoplasmosis causes focal chorioretinal scars in immunocompetent individuals and does not require antimicrobial therapy. In immunosuppressed individuals, *Histoplasma capsulatum* may cause multifocal white lesions in one or both eyes and several case reports of disseminated *Histoplasma* causing endogenous endophthalmitis have been reported in patients with acquired immunodeficiency syndrome (AIDS). Treatment of endogenous

endophthalmitis caused by *Histoplasma* is with intravenous and intravitreal amphotericin B as described above for (include the regimen/dose as above…for example, "described above for Blastomyces") [133, 134].

## Special considerations for children and pregnant women

Two groups of patients need special attention—children and pregnant women.

### Endophthalmitis in pregnancy

Endogenous endophthalmitis during pregnancy is rare and data are limited. Penicillin, cephalosporins, and erythromycin are the mainline agents due to good safety profiles. Fluoroquinolones have been associated with abnormalities of developing cartilage in animal studies and should be avoided if there are safer alternatives. Among the antifungals, voriconazole should be completely avoided, while other azoles can be used for a short period [135]. Intravitreal injections of amphotericin B are considered safe and do not have significant systemic absorption or side effects [135].

### Pediatric endophthalmitis

Pediatric endophthalmitis is also uncommon. Most often, it occurs following penetrating eye trauma and less commonly due to septicemia or intraocular surgeries. *Staphylococcus* and *Streptococcus* species are common bacterial etiologies of post-traumatic and post-operative endophthalmitis, whereas *Candida* is a common cause of endogenous endophthalmitis [136]. Treatment involves prompt intravitreal injection of vancomycin and ceftazidime ± amphotericin B, depending on clinical suspicion for fungal endophthalmitis. Systemic voriconazole is generally not recommended in children because voriconazole pharmacokinetics are unpredictable; it is difficult to attain target concentration, and therapeutic drug monitoring with repeated blood draws is very challenging in children < 6 years old [137]. When possible, fluconazole should be used instead of voriconazole in children. The recommended dose for fluconazole is 12 mg/kg oral or intravenous (loading), followed by 6 mg/kg every 24 to 48 h, depending on the age of the child (younger patients require less frequent dosing) [138].

Systemic therapy with fluoroquinolones may be necessary for prophylaxis in cases of penetrating open-globe injury or for the treatment of post-traumatic endophthalmitis. There is trepidation against the use of fluoroquinolones in pediatric patients, which stems from early preclinical studies with first-generation quinolones that demonstrated damage to articular cartilage in weight-bearing joints of Beagle dogs. This adverse effect continues to limit fluoroquinolone use in pediatric patients' consequent to concern that similar effects might occur in growing children. Several large retrospective studies have been performed evaluating the adverse effects observed with fluoroquinolone use in children. Yee et al. [139] performed a retrospective analysis of over 6000 children with a history of fluoroquinolone use and a "control group" of children exposed to azithromycin. The calculated risk of tendon or joint disorders was not different in the fluoroquinolone versus control groups. Noel et al. [140] examined the safety profile of levofloxacin in a cohort of 2523 children from three large multi-center efficacy trials. Although self-reported rates of musculoskeletal events (arthritis, arthralgia, tendinopathy) were higher in the levofloxacin-treated group compared to the non-fluoroquinolone group, the symptoms were transient, self-resolving, and computed tomography (CT) or magnetic resonance imaging (MRI) did not reveal any apparent joint abnormalities. Thus, despite concerns of possible adverse effects, fluoroquinolones continue to be used in infants and children for the treatment of pneumonia, especially secondary to cystic fibrosis, infections associated with genitourinary abnormalities, infections in immunosuppressed patients, or infections secondary to multidrug-resistant organisms. Given their excellent bioavailability, activity against many causative agents of endophthalmitis, including *Pseudomonas*, and good intravitreal penetration, moxifloxacin, or levofloxacin should be considered as adjuvant therapy to intravitreal injections for treatment of pediatric endophthalmitis. Infants and young adults have a faster clearance of levofloxacin, and thus, the recommended dose is levofloxacin 10 mg/kg BID for children younger than 12 years old and 10 mg/kg daily for adolescents and adults older than 12 years [141]. Oral and intravenous doses of the drug achieve similar plasma concentrations. The recommended dose for moxifloxacin is 400 mg oral/intravenous daily.

## Emerging new therapies

The mainstay of treatment of bacterial endophthalmitis is intravitreal vancomycin and ceftazidime or amikacin. It is worth noting that intraocular vancomycin has been associated with the rare entity hemorrhagic occlusive retinal vasculitis (HORV). All reported cases of HORV arose after a bolus intracameral injection of vancomycin during cataract surgery [142, 143]. Disease course and findings suggest that HORV is a delayed hypersensitivity reaction to vancomycin so future intravitreal vancomycin injection should be avoided.

An intriguing alternative to antibiotics is the use of intravitreal dilute povidone-iodine (PI). The vitreous PI concentration of 0.013 to 0.027% has been shown to be safe for the ocular tissues in animal models of endophthalmitis. Tanaka et al. report a case of endogenous endophthalmitis treated with intravitreal injection of 1.25% PI (prepared by mixing 0.1 mL of undiluted 10% PI with 0.7 mL sterile balanced salt solution)

in addition to systemic intravenous antibiotics [144]. Several others have shown good clinical outcomes in post-operative endophthalmitis treated with intravitreal 1.25% PI injection followed by vitrectomy using 0.025% PI in the irrigating solution [145, 146]. More research is needed to determine the safety and efficacy of dilute PI as an alternative or adjunct to intravitreal antibiotics. It may be a good alternative in resource-poor communities or in cases of multidrug-resistant infections.

## Viral retinitis and chorioretinitis

Viruses of the herpes virus family, namely herpes simplex virus-1 and herpes simplex virus-2 (HSV-1, HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), can cause varying severity of retinitis and chorioretinitis. Treatment almost always involves a prolonged duration of intravitreal and systemic antiviral agents. The antiviral treatment regimen is summarized in Table 3.

### Acute retinal necrosis

Acute retinal necrosis (ARN) is characterized by panuveitis with retinal necrosis. It is most commonly caused by HSV-1, HSV-2, VZV, and rarely EBV. Treatment requires both intravitreal injections of antiviral agents and systemic therapy to inhibit viral replication and halt disease progression in the affected eye and prevent involvement in the unaffected eye. Various options exist for systemic therapy, including intravenous and oral acyclovir, oral valacyclovir, famciclovir and valganciclovir, and intravenous foscarnet and ganciclovir. Historically, ARN was treated with intravenous acyclovir (10–15 mg/kg TID) for 5–10 days and then transitioned to oral acyclovir (800 mg 5 times/day) for 4–6 weeks [147]. This is still a viable and well-studied option for many patients. Side effects of acyclovir include CNS toxicity, lethargy, delirium, and renal toxicity.

With the advent of other oral agents with better pharmacokinetics, val-esters are now the preferred first-line therapy for ARN. Specifically, oral valacyclovir 1 g TID achieves plasma levels similar to intravenous acyclovir and has excellent vitreous penetration to inhibit the replication of HSV-1, HSV-2, and VZV [34]. Several case series report successful treatment of ARN and prevention of second eye involvement when treated with oral valacyclovir [148–150]. A treatment minimum duration of 6 weeks with a systemic antiviral agent is recommended. A major side effect of valacyclovir is a hemolytic uremic syndrome.

Oral famciclovir 500 mg TID for 12 weeks, followed by a taper for 13 weeks, maybe an alternative for ARN resistant to traditional acyclovir therapy and it too achieves vitreous concentration sufficient to inhibit HSV-1, HSV-2, and VZV [151]. Famciclovir is well tolerated and has minimal side effects.

Lastly, intravenous foscarnet can be used for the treatment of ARN, but it is usually reserved for patients who have failed other antiviral therapy. Foscarnet is a direct DNA polymerase inhibitor and does not depend on viral thymidine kinase, making it more effective in treating resistant strains. Foscarnet resistance is extremely rare in immunocompetent individuals. There are case reports of intravenous foscarnet 150 mg/kg being used to treat HSV-2-related ARN resistant to acyclovir and ganciclovir therapy [152, 153].

In addition to the above systemic antiviral therapy, intravitreal injection of either foscarnet 2.4 mg/0.1 mL or ganciclovir 2 mg/0.1 mL is recommended in all patients with ARN. In two comparative small studies, a combination of intravitreal and intravenous therapy showed a decreased incidence of retinal detachment and severe vision loss compared to systemic therapy alone [154, 155]. The mean inhibitory concentration for herpes viruses was reached 60 h and 36 h after treatment with intravitreal ganciclovir and intravitreal foscarnet, respectively [156]. Repeat intravitreal injections can be administered every 2–3 days as deemed necessary by clinical exam. Prophylactic laser demarcation to reduce the risk of detachment is controversial and outside the scope of this discussion.

### Progressive outer retinal necrosis

Progressive outer retinal necrosis (PORN) is a devastating infection of the retina, usually caused by VZV in severely immunocompromised hosts, particularly those with AIDS. It is characterized by deep retinal opacification, fewer inflammatory signs than ARN, a poor response to antiviral agents, and rapid progression to bilateral visual loss. The mainstay of treatment is immune reconstitution with highly active antiretroviral therapy (HAART), combination systemic antivirals to halt viral replication and prevent involvement of the unaffected eye [157], and frequent intravitreal injections and/or implants [158]. The exact combination of antiviral agents and the total time for intravenous therapy is not known. The traditional treatment for VZV is acyclovir; however, patients with AIDS have been frequently treated with prophylactic oral acyclovir, and thus, when they develop VZV retinitis, acyclovir may not be adequate and hence, other antiviral agents are necessary. In addition, the total duration of treatment is difficult to determine and should be individualized. Since PORN occurs in immunosuppressed individuals, antiviral therapy should be continued at a maintenance level until immune recovery is established. However, the level of immune recovery at which antiviral therapy in PORN may be safely discontinued has not been established. More evidence exists in the literature related to the treatment of CMV retinitis, in which most practitioners consider CD4 T-lymphocyte counts

**Table 3** Antiviral treatment regimen for viral chorioretinitis

| Category | First-line treatment | Alternative | Duration* |
|---|---|---|---|
| Acute retinal necrosis (ARN) | • Intravitreal foscarnet 2.4 mg/0.1 mL OR intravitreal ganciclovir 2 mg/0.1 mL<br>PLUS<br>• Intravenous acyclovir 10–15 mg/kg TID OR oral valacyclovir 1 g TID<br>• Oral corticosteroids can be initiated 24–48 h after antiviral therapy | For acyclovir- and ganciclovir-resistant ARN,<br>• Intravenous foscarnet 40 mg/kg TID | Transition to oral acyclovir 800 mg 5 times/day, oral valacyclovir 1 g TID, or oral famciclovir 500 mg TID for 3–4 months upon resolution of vitritis |
| Progressive outer retinal necrosis (PORN) | Immune reconstitution for patients with HIV<br>• Intravitreal foscarnet 1.2 mg/0.05 mL and ganciclovir 2 mg/0.05 mL<br>PLUS<br>• Intravenous foscarnet 90 mg/kg BID AND intravenous ganciclovir 5 mg/kg BID | Intravitreal ganciclovir 2 mg/0.1 mL alone has been used to treat PORN | Systemic therapy until CD4 count > 100 cells/μL.<br>Intravitreal injections are repeated twice a week until immune reconstitution. |
| Cytomegalovirus (CMV) | Immune reconstitution for patients with HIV<br>• Induction therapy with either<br>– Intravenous ganciclovir 5 mg/kg BID for 2–3 weeks<br>OR<br>– Intravenous foscarnet 60 mg/kg TID for 2–3 weeks<br>OR<br>– Oral valganciclovir 900 mg BID for 3 weeks<br>• Intravitreal ganciclovir 2 mg/0.1 mL if zone I CMV retinitis twice weekly, followed by once a week. | All antiviral agents have equal efficacy in treating CMV. | Maintenance therapy until CD4 count > 100 cells/μL for at 6 months with either<br>– Oral valganciclovir 900 mg daily |

*Duration of therapy is only a starting guide and should be adjusted based on the clinical course

greater than 100 cells/μL as a safe level to stop maintenance treatment. Given the lack of well-accepted guidelines, we highlight a few case series of successful treatment of PORN.

Kim et al. [159] reported successful treatment of PORN with good long-term preservation of vision with a ganciclovir implant, weekly intravitreal injections of foscarnet (2.4 mg/0.1 mL) for 5 weeks, and intravenous acyclovir, which was transitioned to oral valacyclovir 1 g TID until CD4 > 100 cells/μL. The ganciclovir implant (discussed further in Cytomegalovirus retinitis) is approved for the treatment of CMV retinitis and although its efficacy in VZV-PORN is unproven, it may reduce the risk of CMV retinitis. Similarly, Yin et al. [160] reported a case of VZV-PORN treated with intravenous foscarnet (90 mg/kg BID), intravenous ganciclovir (5 mg/kg BID), and twice-weekly intravitreal injections of ganciclovir (2 mg/0.05 mL) and foscarnet (1.2 mg/0.05 mL). Tapering intravitreal injections to once a week caused re-exacerbation of PORN and this patient required a total of 58 intravitreal injections [160].

Although most authors would argue that both systemic and intravitreal antivirals should be employed, Spaide et al. treated 6 patients with VZV-PORN with a combination of intravenous acyclovir PLUS ganciclovir or intravenous foscarnet PLUS ganciclovir [157]. In contrast, Gore et al. [161] employed only intravitreal injections of ganciclovir (twice weekly for 2 weeks, then once a week until CD4 > 100 cells/μL) and HAART therapy to treat a larger cohort of 39 patients. Given the lack of large comparative studies, we recommend treatment with a combination of systemic and local/intravitreal antiviral therapy.

## Cytomegalovirus retinitis

Cytomegalovirus (CMV) retinitis usually occurs in immunocompromised hosts with AIDS, renal allografts, systemic malignancies, or patients receiving high-dose corticosteroids. In individuals with AIDS, the risk of CMV retinitis is significantly elevated when the CD4 count is less than 100 cells/μL. Approximately 30% of patients with AIDS will develop CMV retinitis. The clinical diagnosis is made by demonstrating the virus in the patient's urine or by polymerase chain reaction (PCR) for CMV from the aqueous or vitreous fluid.

Immune reconstitution with HAART is paramount for CMV retinitis treatment in individuals with AIDS, especially because ocular penetration of systemically administered anti-CMV agents is moderate [36]. Treatment consists of systemic antiviral therapy with a 2–3 week period of high-dose administration to stop viral replication (induction period), followed by lower-dose therapy to suppress viral activity (maintenance period). Induction therapy for CMV retinitis is usually with one of four available drugs: intravenous ganciclovir, intravenous foscavir, intravenous cidofovir, oral valganciclovir, or surgical placement of an intravitreal ganciclovir implant. Studies comparing ganciclovir to foscarnet or cidofovir have failed to show a significant benefit of one particular agent.

Historically, ganciclovir has been the treatment of choice, with 80–90% showing resolution of retinitis following induction dosages of intravenous ganciclovir. The typical induction regimen for ganciclovir is 5 mg/kg intravenous BID for 2–3 weeks and then maintenance with 5 mg/kg daily [162]. At this dose, ganciclovir has moderate intravitreal penetration but achieves intravitreal concentration that are just below the $ID_{90}$ [36]. The $ID_{90}$ of ganciclovir is 7.9–10.0 μM and $ID_{90}$ of foscarnet is 300–500 μM. Arevalo et al. measured the intravitreal concentrations of ganciclovir and foscarnet after receiving induction dose intravenous therapy in 52 AIDS patients with CMV retinitis and found a mean vitreal ganciclovir concentration 4.74 ± 1.49 μM and foscarnet concentration 189 ± 177 μM [36]. Intravitreal concentration did not increase despite increasing the dose of systemic therapy. The subtherapeutic levels of these antiviral agents may partly explain why patients require long-term maintenance therapy to keep the infection under control until the host immune system is restored and able to eliminate the virus.

The sustained-release ganciclovir implant (Vitrasert, Bausch + Lomb, Rochester, New York) may be substituted for intravenous ganciclovir and it has demonstrated clinical success in the treatment of CMV retinitis. The implant was approved by the Food and Drug Administration for the treatment of CMV retinitis in AIDS patients in 1996 but has been discontinued since 2013. We include a brief description of this implant for a historical perspective only as it is no longer manufactured. This implant releases ganciclovir from a 4.5 mg capsule at a rate of 1 μg/h for up to 9 months, although replacement is recommended around week 32 to avoid the risk of recurrence when the implant empties [163–165]. However, unless patients with the ganciclovir implant also receive systemic anti-CMV therapy, they are at a continued high risk of developing both contralateral retinitis and extra-ocular CMV disease. A major side effect of systemic ganciclovir is bone marrow suppression and historically, there was apprehension in its use in individuals taking zidovudine (AZT). However, AZT is no longer the standard treatment of HIV and growth factors such as filgastim are now available to support bone marrow leukopoiesis.

More recently, valganciclovir has become the drug of choice for most patients due to its lower cost, oral administration, and improved intravitreal penetration compared to the other agents. In a study comparing oral valganciclovir to intravenous ganciclovir, there was no significant difference between the two agents for induction therapy [37]. Maintenance therapy with valganciclovir can be discontinued after achieving CMV retinitis quiescence and CD4 count persistently greater than 100–150 cells/$mm^3$ for at least 6 months [166, 167]. The induction dose for valganciclovir is 900 mg twice a day for 3 weeks, followed by 900 mg once a day for maintenance.

In patients' unresponsive to ganciclovir or relapsed CMV retinitis in patients with AIDS, combination treatment with intravenous foscarnet and ganciclovir may be useful [168]. The recommended regimen for foscarnet is 60 mg/kg intravenous TID for 2–3 weeks (induction) and then 30–40 mg/kg intravenous TID (maintenance). Lastly, cidofovir was historically used to treat CMV retinitis since it was the least expensive intravenous regimen and required infrequent dosing. However, it is no longer manufactured due to a decreasing incidence of CMV retinitis in adults with AIDS.

In addition to systemic antiviral therapy, intravitreal antiviral agents should be administered when CMV retinitis is within 1500 μm of the nerve or within 3000 μm of the fovea (zone I CMV retinitis). Intravitreal ganciclovir 2 mg/0.1 mL is particularly useful in patients with severe neutropenia, in whom further bone marrow suppression with intravenous ganciclovir is a concern. Twice weekly injections are given during the induction phase, followed by weekly injections during maintenance. Intravitreal cidofovir should not be used and there is very limited data on the use of intravitreal foscarnet for treatment of CMV retinitis.

## Other bacterial retinitis and chorioretinitis

Several bacterial infections cause chorioretinitis with or without vitritis. These include the causative agent of tuberculosis, cat scratch disease, and Whipple's disease. The treatment regimen is summarized in Table 4.

### Tuberculosis

Tuberculosis (TB) is a systemic disease caused by *Mycobacterium tuberculosis* (MTB). Ocular manifestations include anterior granulomatous uveitis, intermediate uveitis with vitritis, snow banking and peripheral chorioretinal granulomas or choroidal tubercles, retinal vasculitis, and subretinal abscess. Immunocompromised patients may develop a multifocal retinochoroiditis [169]. Intraocular TB is a great mimicker of various uveitis entities and it can be considered on the differential diagnosis of any intraocular inflammation.

Diagnosis can be often challenging given the wide spectrum of presentation. A definitive diagnosis is made when MTB can be visualized or cultured from the involved tissue—this is generally not possible with a uveal biopsy. Thus, indirect evidence and laboratory tests can aid in the diagnosis of presumed ocular TB. Most patients with ocular TB do not have a history of pulmonary TB or other systemic TB so the absence of pulmonary TB does not rule out ocular TB. Diagnostic tests include tuberculin skin test, interferon-gamma release assay, and molecular tests. The tuberculin skin test is the oldest of the three and has been used for several decades to detect latent TB. It consists of

**Table 4** Antimicrobial treatment regimen for other bacterial causes of chorioretinitis

| Category | first-line treatment | Alternative | Duration |
|---|---|---|---|
| Tuberculosis | • Four-drug regimen, given daily: oral isoniazid 5 mg/kg, rifampin 10 mg/kg, pyrazinamide 25 mg/kg and ethambutol 15 mg/kg for the first 2 months and continued treatment on 2 drugs isoniazid and rifampin for total 18 months<br>• Topical or oral corticosteroids for uveitis or retinal vasculitis | Alternative treatment regimen is guided by tuberculosis resistance patterns. | Quadruple drug therapy for 2 months, then dual drug therapy for additional 16 months, for total 18-month treatment duration |
| Cat scratch disease | • Oral doxycycline 100 mg BID ±<br>• Oral rifampin 300 mg BID to TID | May substitute doxycycline for erythromycin 500 mg QID in young children | Systemic antimicrobial therapy for 4–6 weeks. If erythromycin is used, the treatment duration is 3 months. |
| Whipple's disease | • Intravenous ceftriaxone 2 g BID for 2–4 weeks, then<br>• Oral TMP/SMX 160/800 mg BID PLUS<br>• Oral rifampin 600 mg daily | Intravenous ceftriaxone may be omitted. | TMP/SMX and rifampin are continued for at least 1 year to adequately treat and prevent relapses. |

*TMP/SMX*, trimethoprim/sulfamethoxazole; *BID*, twice daily; *TID*, three times daily; *QID*, four times daily

an intradermal injection of 5 units of purified protein derivative and induration of > 15 mm after 48–72 h is considered positive in persons with no known risk factors for TB. Guidelines for interpreting tuberculin skin test vary in different countries where different strengths are used and the predictive value of the test varies depending on the incidence of TB in the population. In the USA, where the incidence of TB-associated uveitis is low, a positive purified protein derivative test result in a patient with uveitis has less than 1% likelihood of having tuberculosis [170]. Instead, interferon-gamma release assay (IGRA) has greater specificity than tuberculin skin testing [171]. IGRA is based on detecting gamma interferon production by T cells that are sensitized to antigens specific to MTB. Accuracy of diagnosis of ocular TB increases when both IGRA and tuberculin skin test are used in combination [172]. Lastly, molecular techniques such as polymerase chain reaction (PCR) to identify MTB DNA or detection of antibodies against purified cord factor (an abundant cell wall component of MTB) in the aqueous or vitreous fluid sample may provide strong evidence of the infection [173]. However, oftentimes, the ocular manifestations of MTB represent delayed immunologic hypersensitivity reaction, rather than a direct mycobacterial infection, making the analysis of aqueous/vitreous fluid sample less sensitive [174, 175].

Recommended treatment for all patients with ocular TB is four-drug therapy with isoniazid 5 mg/kg, rifampicin 10 mg/kg, pyrazinamide 25 mg/kg, and ethambutol 15 mg/kg. These are given once daily for the first 2 months and treatment is then continued with isoniazid and rifampicin for a total of 18 months [169, 176]. However, given the rise of multidrug-resistant strains, antibiotic susceptibilities and consultation with an infectious disease specialist are important for proper antibiotic selection. Both 9- and 12-month treatment regimens are inadequate as relapses have been observed with shorter duration of therapy [177]. In addition, topical steroids, as well as oral corticosteroids at a dose 0.5–1 mg/kg, tapered slowly over 9–12 months can be used as an adjuvant to treat vasculitis or uveitis.

A unique situation often arises when treating patients with uveitis, not caused by active TB that have a positive tuberculin skin test (i.e., latent TB). It is recommended that patients with latent TB are treated with any of the following: (1) isoniazid 300 mg/day for 9 months (preferred for patients with HIV, pregnant women, or children), (2) rifampicin 10 mg/kg daily for 4 months, or (3) isoniazid and rifapentine once weekly for 3 months. Rifapentine dose is bracketed by body weight: 300 mg (10.0–14.0 kg body weight), 450 mg (14.1–25.0 kg body weight), 600 mg (25.1–32.0 kg body weight), 750 mg (32.1–49.9 kg body weight), and 900 mg (> 50.0 kg body weight). Consultation from an infectious disease specialist is often recommended prior to initiating treatment.

Ocular side effects of TB medications should be considered and monitored. Ethambutol causes dose-dependent toxicity (if the daily dose exceeds 25 mg/kg or more), which includes optic neuritis, red-green dyschromatopsia, and disc edema/hyperemia [178]. Isoniazid can rarely cause optic neuropathy. Rifabutin, when combined with clarithromycin, can cause anterior uveitis, corneal endothelial deposits, and vitreous opacities, which respond well to topical steroids [179]. The role of intravitreal injections in the treatment for ocular TB has not been established.

## Cat scratch disease

Cat scratch disease (CSD) is caused by a pleomorphic Gram-negative bacillus, most commonly due to the *Bartonella* species. Fundoscopic findings include focal white retinal and optic disc lesions, swelling of the optic disc, and a macular star. Occasionally, severe occlusive vasculitis can occur [180, 181]. Diagnosis is confirmed with positive serology for *Bartonella henselae*. Ocular manifestations are usually self-limited and treatment is indicated only for patients with severe vision loss or in immunocompromised hosts. When clinically indicated, a 4- to 6-week course of oral doxycycline 100 mg BID is used. Oral rifampin 300 mg BID to TID may be added to shorten the course of infection and hasten visual recovery [182, 183]. In children younger than 8 years of age, oral erythromycin 500 mg QID for 3 months may be an acceptable alternative to doxycycline, although erythromycin does not have as good intraocular penetration as doxycycline [183]. Doxycycline may still be used in children with caution when there are no acceptable alternatives (see further discussion in section 5.8).

## Whipple's disease

*Tropheryma whipplei*, the causative agent of Whipple's disease, is a Gram-negative actinomycete that causes a chronic multisystem disease characterized by fever, diarrhea, steatorrhea, arthralgia, cardiac murmur, and lymphadenopathy. Ocular findings include vitreous opacities, retinal hemorrhages, cotton-wool spots, chorioretinitis, and retinal vasculitis [184]. Diagnosis is confirmed with either duodenal or jejunal biopsy. The recommended treatment is ceftriaxone 2 g intravenous BID for 2 to 4 weeks, followed by TMP-SMX 160/800 mg oral BID and rifampin 600 mg oral daily for at least 1 year to adequately treat and prevent relapses [185]. Intravenous ceftriaxone was omitted in a study by Touitou et al. [186] and patients were successfully treated with combination oral TMP-SMX and rifampin. The average time to control ocular inflammation on oral antibiotic therapy was about 3 months [186].

## Spirochetes and tick-borne diseases

Several spirochetes and tick-borne diseases can also cause chorioretinitis. The treatment regimen is summarized in Table 5.

### Ocular syphilis

Syphilis is caused by the spirochete *Treponema pallidum*. It can present in various forms within the eye, including, but not limited to, uveitis and chorioretinitis. Ocular syphilis with chorioretinitis or vitritis is a form of neurosyphilis. Recommended treatment by the Center for Disease Control and Infectious Diseases Society of America (IDSA) is:

- Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units intravenous every 4 h for 10–14 days or
- Procaine penicillin G 2.4 million units intramuscular once daily PLUS probenecid 500 mg orally QID, both for 10–14 days [187]

Both strategies have been used to successfully treat ocular syphilis. Testing for HIV is recommended in all patients with syphilis and treatment duration in HIV-positive individuals is 3 weeks. In many cases of ocular syphilis, there is an accompanying uveitis for which topical steroids may be judiciously used.

It is important to note that oral penicillin or oral penicillin alternatives have not demonstrated efficacy in the treatment of ocular syphilis. Similarly, benzathine penicillin, commonly used for latent or tertiary syphilis, does not cross the blood-brain barrier and should not be used for neurosyphilis [188, 189].

In patients with a penicillin allergy, there is limited data that ceftriaxone 2 g daily either intravenous or intramuscular for 10–14 days can be used as an alternative [190]. However, there is some cross-reactivity between cephalosporins and penicillin and if there is a high concern for a life-threatening allergy, skin-prick testing can be performed to determine whether a true allergy exists. Penicillin desensitization is the preferred route of treatment for neurosyphilis for individuals allergic to penicillin and especially for pregnant women who are penicillin allergic.

### Lyme disease

Lyme borreliosis is a tick-borne disease caused by the spirochete *Borrelia burgdorferi*. Various fundoscopic changes have been reported in patients with serologic evidence of prior exposure to *B. burgdorferi*, including pars planitis, retinal vasculitis, choroiditis, macular edema, and papilledema. Ocular involvement in systemic borreliosis is uncommon (incidence of 1–4%) and given the lack of sufficient data, the IDSA does not make specific recommendations for treatment of ocular borreliosis. However, neurologic manifestations of Lyme disease are treated with intravenous ceftriaxone 2 g daily for 10–28 days (average 14 days). Alternatively, oral doxycycline 200–400 mg per day in 2 divided doses for 10–28 days, intravenous cefotaxime 2 g TID, or intravenous penicillin G 18–24 million units per day divided into 6 doses for 2–3 weeks are all acceptable alternatives [191]. When faced with pars planitis with snowbank formation or anterior uveitis in a patient with serologic evidence of *B. burgdorferi*, it is reasonable to treat with topical steroids and systemic therapy as outlined above.

### Rocky Mountain spotted fever

*Rickettsia rickettsii* is a Gram-negative bacterium transmitted by the wood and dog tick and is the infectious agent for Rocky Mountain spotted fever (RMSF). Ocular findings include petechial lesions of the bulbar conjunctiva, anterior uveitis, papilledema, retinal venous engorgement, retinal hemorrhages, and retinal vascular occlusion [192–195]. Doxycycline is the antibiotic of choice for adults and children. Previous concerns about tooth staining in children younger than 8 years treated with doxycycline stem from experience with older tetracycline class drugs that bind more readily to calcium than newer members of the drug class, such as doxycycline. Doxycycline used at the dose and duration recommended for treatment of RMSF in children aged < 8 years, even after multiple courses, did not result in tooth staining or enamel hypoplasia in a 2013 retrospective cohort study [196]. The recommended dosage of doxycycline is 100 mg oral or intravenous BID for adults and 2.2 mg/kg oral or intravenous BID for children that weigh less than 100 pounds. A 5- to 7-day course is recommended [197].

The use of tetracycline class drugs has generally been contraindicated in pregnancy because of concerns about the potential risk to the musculoskeletal development of the fetus, cosmetic staining of the teeth, and acute fatty liver of pregnancy in the mother. Again, these adverse effects were observed with older tetracycline derivatives and the cautionary "contraindication" has carried to newer tetracycline agents such as doxycycline. A recent systematic review reported no evidence of teratogenicity or maternal hepatic toxicity associated with doxycycline use during pregnancy; however, no controlled trial exists to definitively characterize the risk [198]. Patient counseling and discussion of risks and benefits ultimately will guide the decision to treat with doxycycline.

## Parasites and worms

Several zoonotic organisms can cause infections of the posterior segment. The treatment regimen is summarized in Table 5.

**Table 5** Antimicrobial treatment regimen for spirochetes, parasites, worms, and tick-borne diseases

| Category | First-line treatment | Alternative | Duration* |
|---|---|---|---|
| Syphilis | • Intravenous aqueous penicillin G 3–4 million units every 4 h | If penicillin allergy,<br>• Penicillin desensitization is recommended.<br>• Intravenous or intramuscular ceftriaxone 2 g daily 10–14 days may be an alternative but not generally recommended. | Treatment with penicillin G for 10–14 days. In patients with HIV, treatment is continued for 3 weeks. |
| Lyme disease | • Intravenous ceftriaxone 2 g daily | • Oral doxycycline 200–400 mg BID<br>OR<br>• Intravenous cefotaxime 2 g TID<br>OR<br>• Intravenous penicillin G 18–24 million units daily | Antibiotic treatment for 10–28 days |
| Leptospirosis | • Intravenous ceftriaxone 1 g daily | • Intravenous penicillin G 1.5 million units every 4 h | Antibiotic treatment for 7 days |
| Toxoplasmosis | • Oral pyrimethamine 100 mg on day 1, then 50 mg daily, PLUS oral sulfadiazine 1 g QID, PLUS oral folinic acid 5–15 mg daily ± oral prednisone 40 mg daily<br>OR<br>• Oral pyrimethamine 100 mg on day 1, then 50 mg daily PLUS oral sulfadiazine 1 g QID PLUS oral clindamycin 300 mg QID ± oral prednisone 40 mg daily<br>OR<br>• Oral TMP/SMX 160/800 mg BID ± oral prednisone 40 mg daily | • Intravitreal clindamycin 1 mg/0.1 mL may be used in fovea-threatening cases in addition to systemic therapy<br>If sulfa-allergy,<br>• Oral pyrimethamine PLUS azithromycin 250 mg daily ± prednisone 40 mg daily | Antimicrobial treatment duration 14–90 days, most are treated for 30 days. |
| Toxocariasis | • Oral albendazole 800 mg BID for adults and 400 mg BID for children<br>Systemic and topical corticosteroids to reduce inflammation, typical prednisone 1 mg/kg daily, and topical prednisolone QID | N/A | Antimicrobial treatment for 7–14 days |
| Cysticercosis | • Oral prednisone 1 mg/kg daily<br>OR<br>• Oral praziquantel 50 mg/kg daily with oral prednisone<br>OR<br>• Oral albendazole 15 mg/kg daily with oral prednisone | Surgical excision of the cyst recommended when possible | Antimicrobial therapy for 15 days |
| Diffuse unilateral subacute neuroretinitis | • Death of the worm by photocoagulation | If mild to moderate vitritis,<br>• Oral thiabendazole 22 mg/kg BID | Antimicrobial therapy for 2–4 days |
| Rocky Mountain spotted fever | • Oral or intravenous doxycycline 100 mg BID for adults; oral or intravenous doxycycline 2.2 mg/kg BID for children | N/A | Antimicrobial therapy for 5–7 days |

*TMP/SMX*, trimethoprim/sulfamethoxazole; *BID*, twice daily; *TID*, three times daily; *QID*, four times daily; *N/A*, not applicable

*Duration of therapy is only a starting guide and should be adjusted based on the clinical course

## Leptospirosis

Leptospirosis is a zoonotic infectious disease caused by a spirochete *Leptospira*. Systemic symptoms include fever, jaundice, hemorrhages, and renal failure. Ocular manifestations can present in both infective and immunologic stages of systemic leptospirosis. The most common ocular manifestation is anterior non-granulomatous uveitis or panuveitis with membranous vitritis and vasculitis [199]. Diagnosis is confirmed by PCR of aqueous or vitreous fluid. Treatment of mild systemic leptospirosis is controversial, but severe cases can be treated with either intravenous ceftriaxone 1 g daily for 7 days or intravenous penicillin G 1.5 million units every 4 h for 7 days [200, 201]. Uveitis is treated with either topical, subtenon, or oral corticosteroids depending on the extent of involvement [199, 202].

## Toxoplasmosis

Toxoplasmosis is the most common cause of posterior uveitis and focal necrotizing retinitis in an otherwise healthy individual. It is caused by the protozoan *Toxoplasma gondii* and is transmitted in utero or less commonly following the ingestion of the organism. Clinical diagnosis of ocular toxoplasmosis is usually presumptive in a healthy individual with a focus of acute retinitis in one eye with one or more chorioretinal scars. Most patients demonstrate serologic evidence of prior exposure with positive IgG titers.

Anti-toxoplasma agents include pyrimethamine, sulfadiazine, clindamycin, trimethoprim-sulfamethoxazole, and azithromycin. There is significant variability among uveitis specialists on when to treat and which antiparasitic agents to use, especially because there is little firm evidence that antimicrobial therapy alters the natural history of toxoplasmic retinochoroiditis in immunocompetent individuals. Treatment is almost always indicated in immunocompromised patients, patients with congenital toxoplasmosis, and pregnant women with the acquired disease. In immunocompetent individuals, the number, size, and location of the chorioretinal lesion relative to the fovea or optic disc and the severity of vitritis may influence the decision to treat with one or more antimicrobial agents in combination with systemic corticosteroids [203]. The typical regimen consists of any of the following:

- Pyrimethamine 100 mg oral on day 1, followed by 50 mg daily, sulfadiazine 1 g oral QID, and folinic acid 5–15 mg PO daily with or without prednisone 40 mg oral daily ("classic therapy").
- Pyrimethamine, sulfadiazine, and clindamycin 300 mg oral QID with or without prednisone ("quadruple therapy).
- Trimethoprim/sulfamethoxazole 160/800 mg oral BID with or without prednisone.

Oral corticosteroids are started after 2–3 days of starting systemic antimicrobial therapy and continued for approximately 1 month with a slow taper. For patients with a sulfadrug allergy, an alternative regimen consisting of pyrimethamine (100 mg on day 1, followed by 50 mg oral daily), azithromycin (250 mg oral daily or 500 mg oral every other day), and folinic acid (15 mg oral daily) achieves similar visual outcomes as the classic regimen and is better tolerated with fewer side effects [204]. The duration of antiparasitic treatment is anywhere from 14 to 90 days (median 35 days), depending on the response to therapy.

Pregnant women with newly acquired toxoplasmosis can be treated with azithromycin, clindamycin, and atovaquone 750 mg oral QID. Sulfonamides can be used safely during pregnancy during the first 2 trimesters. The Society of Obstetricians and Gynecologists of Canada recommends treatment of pregnant women in whom fetal infection has been confirmed or highly suspected with a combination of pyrimethamine, sulfadiazine, and folinic acid [205]. Alternatively, intravitreal clindamycin 1 mg/0.1 mL injection, combined with local periocular corticosteroid injections, can be used in pregnant women to reduce systemic side effects and risk of teratogenicity. Intravitreal clindamycin may also be used in fovea-threatening cases or in patients unresponsive to combination oral antiparasitic therapy [206]. In one small study, treatment with a single intravitreal injection of clindamycin was associated with resolution of vitreous inflammation within 6 weeks in five of six patients (and the sixth patient required a second injection for quiescence) [206]. All patients were previously treated with oral agents prior to intravitreal injection.

## Toxocariasis

Toxocariasis is caused by the larval form of the roundworm *Toxocara canis*. Its clinical presentation can be one of three: posterior pole granuloma, peripheral granuloma, or nematode endophthalmitis. It typically occurs in otherwise healthy children or young adults. The diagnosis of a subretinal granuloma caused by *Toxocara* is presumptive, supported by eosinophilia and confirmed with serum serologies. The standard treatment of ocular toxocariasis is systemic and topical corticosteroid in patients with active intraocular inflammation. The role of antihelminthic therapy is unclear since intraocular pharmacokinetics and pharmacodynamics studies of antihelminthic agents have not been performed. Several authors report visual improvement without recurrence with a combination of corticosteroid and oral albendazole therapy, compared to corticosteroid therapy alone [207, 208]. The recommended dose for

albendazole is 800 mg BID for adults and 400 mg BID for children for 7–14 days.

### Cysticercosis

Cysticercosis is caused by the human ingestion of the eggs of the pork tapeworm, *Taenia solium*. The eggs disintegrate in the gastrointestinal tract; the embryos invade the intestinal wall and are carried throughout the body as the larvae form. The larvae form cysts in the brain and in the eye. Ocular manifestations include extra-ocular muscle, subconjunctival, intraretinal or subretinal cysts, eyelid nodule, papilledema, and/or proptosis and restriction of eye movements [209, 210]. The diagnosis of cysticercosis is based mainly on orbital imaging. Surgical excision of subconjunctival or eyelid lesions is the preferred treatment as the death of the organism elicits an intense inflammatory reaction [211, 212]. Antihelminthic agents have an unknown role in the treatment of cysticercosis. A randomized trial comparing oral prednisone (1 mg/kg daily for 15 days) alone, versus praziquantel (50 mg/kg daily for 15 days) with prednisone versus oral albendazole (15 mg/kg daily for 8 days) with prednisone, did not find significant differences in cyst burden [213].

### Diffuse unilateral subacute neuroretinitis

Diffuse unilateral subacute neuroretinitis (DUSN) is caused by two species of nematodes: a smaller one thought to be the larva of the dog hookworm (*Ancylostoma caninum*) and a larger larva of a raccoon roundworm (*Baylisascaris procyonis*). The clinical syndrome is characterized by vitritis, papillitis, retinal vasculitis, and retinal vessel narrowing with diffuse retinal pigment epithelial degeneration [214]. Given such a diverse set of findings, it can simulate various disorders, including retinal sarcoidosis, acute multifocal posterior placoid pigment epitheliopathy, or multiple evanescent white dot syndrome. The diagnosis is made on clinical examination by identification of the worm (often a painstaking task). The nematode varies in length from 400 to 2000 μm and it moves in the subretinal space. It is most commonly found in the vicinity of active deep retinal white lesions that may be caused by a toxic inflammatory reaction to material left in the wake of a moving nematode [192].

Treatment is the death of the worm by photocoagulation. However, the worm can be difficult to find, and the larger *Baylisascaris* worm moves rapidly, making it difficult to immobilize. Oral antihelminthic agents have limited utility. When the worm is in the subretinal space, the worm is isolated from the effects of oral thiabendazole, although thiabendazole can penetrate the eye in the setting of limited vitritis. Gass et al. [215] reported successful treatment of three patients with DUSN and moderate to severe vitritis, with oral thiabendazole 22 mg/kg BID for 2 to 4 days (maximum dose 3 g). When the worm cannot be found, an alternative strategy to increase ocular penetration of thiabendazole is to first apply a scatter laser around and within the zone of the outer retinal white lesions to disrupt the blood-retina barrier and then give oral thiabendazole. This strategy was initially proposed by Gass and later employed by Gupta et al. [216] to successfully eradicate the worm.

## Pneumocystis jiroveci

*Pneumocystis jiroveci*, previously known as *Pneumocystis carinii*, is a yeast-like fungus that is a normal commensal organism of the pulmonary system but can become pathogenic in patients with humoral and cell-mediated immune deficiency, especially in patients with AIDS. In the eye, *P. jiroveci* causes multifocal placoid or slightly elevated, yellow-white choroidal lesions. These may be mistaken for lesions of large cell lymphoma, sarcoidosis, or Dalen-Fuchs nodules. Ocular involvement is more common in AIDS patients receiving prophylactic aerosolized pentamidine therapy as it does not protect against extrapulmonary disease. Hence, immunocompromised individuals should also be on systemic oral TMP-SMX 160/800 mg prophylaxis once a day. Cases of ocular *P. jiroveci* have decreased dramatically with routine prophylaxis and only two cases have been reported in the past decade in the USA. Ocular involvement indicates a disseminated infection and the recommended treatment is with cotrimoxazole, given at a total daily dose of 20 mg/kg of trimethoprim and 100 mg/kg of sulfamethoxazole in 2–4 divided doses, either intravenous or oral for 21 days followed by continuous prophylaxis at dose 160/800 mg once a day. The second-line therapy is intravenous pentamidine, at a daily dose of 4 mg/kg for 21 days, for patients who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5 to 7 days of TMP-SMX therapy [217–219].

## Conclusion

The purpose of this review article is to provide a comprehensive reference guide for the management of infectious posterior segment diseases. Many infections of the posterior segment have been studied in great detail and there are several well-defined guidelines based on large and randomized studies, although there are not clear guidelines for all diseases. Case reports and case series are sometimes the only data used to provide guidance for treatment of some uncommon infections. We summarize the current literature on the appropriate antimicrobial treatment regimen for the majority of infections of the posterior segment.

Several common threads emerge in treating infections of the posterior segment. Accurate diagnosis via blood culture or

aqueous or vitreous aspirate (preferably before instituting antimicrobial agents) is essential. The empiric broad-spectrum regimen can be narrowed based on antibiotic susceptibilities and local resistance patterns. For particular conditions, patients should be managed in consultation with an infectious disease specialist. Severe sight-threatening infections that have the potential to progress rapidly or with dense vitritis or chorioretinal lesions threatening vision (near the macula or optic nerve) require aggressive treatment with both intravitreal and systemic (usually intravenous) combination antimicrobials. Systemic agents with good intraocular penetration are preferred, especially if intravitreal injections are not indicated or available. For some infections, single-agent therapy may carry a risk of insufficient coverage or development of resistance. Duration of therapy for most infections of the posterior segment is usually 7 to 14 days, except in immunocompromised hosts or when the microorganism is indolent when a longer period (up to 1 year) of therapy may be needed. Many posterior segment infections are also associated with significant inflammation; thus, corticosteroids can be used, although generally after at least 24 to 48 h of antimicrobial therapy. Above all else, a heightened level of suspicion, search for a causative organism, and persistence, with consideration of alternative therapies, are crucial when treating a challenging infection of the posterior segment.

## Method of literature search

This review was based mainly on the recent literature during the last 10 years with the inclusion of some older articles related to drug pharmacokinetics. The authors conducted a search of MEDLINE (from 1960 to 2017) and PubMed databases using the following keywords: infectious chorioretinitis, endophthalmitis, acute retinal necrosis, progressive outer retinal necrosis, chorioretinitis + syphilis, tuberculosis, Toxoplasmosis, Histoplasma, Nocardia, Toxocara, Lyme disease, leptospirosis, DUSN, cysticercosis, Rocky Mountain Spotted Fever, and *Pneumocystis jiroveci*. In addition, references quoted in the articles found through these database searches were also included where appropriate. For articles in languages other than English, abstracts were evaluated for clinical relevance and, when appropriate, were also included.

## Compliance with ethical standards

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

**Ethical approval** This study did not involve human subjects or animal models.

**Informed consent** For this type of study, informed consent is not applicable.

**Disclosures** The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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