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Ocular Infection: Endophthalmitis

Stephen G. Schwartz[a], **Harry W. Flynn Jr**[a], **Taraprasad Das**[c], and **William F. Mieler**[b]

[a]Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL

[b]Department of Ophthalmology, University of Illinois College of Medicine at Chicago, Chicago, IL, USA

[c]Department of Ophthalmology, LV Prasad Eye Institute, Hyderabad, India

Abstract

Endophthalmitis is characterized by marked inflammation of intraocular fluids and tissues. Infective endophthalmitis may be categorized by the cause of the infection, which helps predict the underlying etiology and most likely causative organisms. The major category remains acute-onset postoperative endophthalmitis. Infective endophthalmitis is a clinical diagnosis but is confirmed by evaluation of intraocular fluid specimens. The Endophthalmitis Vitrectomy Study offered important guidelines for the initial management of endophthalmitis, and these guidelines remain relevant to this day. Prompt initiation of empiric broad-spectrum antimicrobial therapy is important in achieving best outcomes.

Endophthalmitis is characterized by marked inflammation of intraocular fluids and tissues. Severe visual loss may occur, even with prompt and appropriate diagnosis and treatment. Infective endophthalmitis may be categorized by the cause of the infection and the characteristic timing of clinical signs and symptoms [1]. Categorization helps predict the underlying etiology and most likely causative organisms (table 1).

The major category, representing over 70% of cases, is acute-onset, postoperative endophthalmitis, which is defined as endophthalmitis presenting within 6 weeks of intraocular surgery (fig. 1) [1]. Chronic postoperative endophthalmitis presents more than 6 weeks following intra-ocular surgery and may be associated with cataract surgery [2], glaucoma filtering blebs (fig. 2) [3], corneal sutures [4], the Ex-PRESS mini glaucoma shunt (Optonol, Neve Ilan, Israel) [5] and other devices. Posttraumatic endophthalmitis occurs following open-globe injuries. Endogenous endophthalmitis results from hematogenous spread of systemic infection. Endophthalmitis may be associated with microbial keratitis [6] and following office-based intravitreal injection [7].

Disease Incidence

The reported incidence of acute-onset postoperative endophthalmitis is in the range of 0.036–0.36% of eyes undergoing intraocular surgery [8–10]. Large series of cataract surgeries have reported risks of 0.04% in the USA [11] and 0.07% in India [12]. An earlier survey reported rates of endophthalmitis of 0.2% following secondary intraocular lens (IOL) implantation, 0.2% after glaucoma surgery and 0.03% after pars plana vitrectomy (PPV)

[13]. In the USA, Medicare claims data suggest that the incidence of acute-onset postoperative endophthalmitis may be increasing [14].

The incidence of endophthalmitis following PPV has been the subject of recent study as many surgeons have largely transitioned from 20-gauge transscleral surgery to 23- or 25-gauge transconjunctival surgery. A systematic review of 148,643 surgical cases reported an incidence of 0.046% [15].

One series of open-globe injuries has reported an endophthalmitis rate of 6.8% [16].

The incidence of endophthalmitis following intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors in prospective clinical trials is in the range of 1% per eye (table 2) [17–22] However, these reported rates relate to eyes, not to the number of total injections. In these trials, most eyes underwent a series of injections, so the incidence of endophthalmitis per injection is very low. Large, retrospective case series of intravitreal injections of VEGF inhibitors generally report infection rates in the range of 0.05% or less (table 3) [23–30] although the reported infection rates following off-label intravitreal injection of triamcinolone acetonide, a corticosteroid, are somewhat higher [31, 32].

Risk Factors

In acute-onset, postoperative endophthalmitis, preoperative risk factors include immune compromise (e.g. diabetes mellitus or immunosuppressive medications), chronic blepharitis, disease of the lacrimal drainage system, contaminated eye drops, contact lens wear, a contralateral ocular prosthesis and active infection elsewhere in the body. Intraoperative risk factors include prolonged surgery, secondary IOL implantation, posterior capsular rupture, vitreous loss, iris prolapse, contaminated irrigating solutions or IOL, and a slightly inferotemporal clear corneal incision. Postoperative risk factors include wound leaks and vitreous incarceration in the wound. Using evidence-based medicine criteria, povidone-iodine antisepsis is the only technique to reach category II evidence for the prevention of postoperative endophthalmitis [33].

Some authors have suggested that clear cornea wounds are a risk factor for infection [34, 35], but other series have found no increased endophthalmitis risk or differences regarding the clinical course, causative organisms or visual outcomes following clear cornea cataract surgery [11, 36]. The prevention of acute-onset, postoperative endophthalmitis following cataract surgery is controversial. The European Society of Cataract and Refractive Surgeons (ESCRS) performed a partially masked, randomized, clinical trial of 13,698 patients and reported a statistically significant benefit with the use of intracameral cefuroxime [37]. Despite these results, there is no consensus on the use of intracameral antibiotics, even in European nations [38]. A Cochrane systematic review, including the ESCRS study, reported that ‘the heterogeneity of study designs and modes of antibiotic delivery made it impossible to conduct a formal meta-analysis’ and ‘it is unlikely that additional clinical trials will be conducted to evaluate currently available prophylaxis’ [39].

Risk factors for filtering bleb-associated endophthalmitis include a history of conjunctivitis, contaminated topical glaucoma medications, contact lenses, an inferior filtering bleb, bleb

leakage, bleb manipulations and nasolacrimal duct obstruction [3]. Risk factors for posttraumatic endophthalmitis include delayed primary repair (beyond 24 h), soil-associated injuries, retained intraocular foreign bodies and breach of the lens capsule [16]. Possible, but unproven, risk factors for endophthalmitis following 25-gauge transconjunctival sutureless vitrectomy include unsutured sclerotomy wounds, vitreous wick syndrome, early postoperative hypotony and increasing use of adjuvants (such as intravitreal triamcinolone acetonide).

The risk of endophthalmitis following small-gauge transconjunctival PPV is apparently not higher than that of 20-gauge transscleral PPV [15].

Endophthalmitis following open-globe injuries is associated with delayed wound closure and lack of prophylactic antibiotic treatment [40]. Retained intraocular foreign bodies are an additional risk factor, especially when associated with vegetable matter exposure or delay to initial management [41].

Risk factors for endogenous endophthalmitis include debilitation, immune compromise and intravenous drug abuse [42]. Endogenous endophthalmitis rarely occurs in infants in a neonatal intensive care unit; reported risk factors include candidemia, bacteremia, retinopathy of prematurity and a low birth weight [43].

Microbial keratitis is very infrequently associated with endophthalmitis, unless associated with corneal perforation, topical corticosteroids, fungal keratitis or keratitis adjacent to a previous surgical wound [44].

There has been much recent investigation regarding risk factors for endophthalmitis following intravitreal injection in terms of compounding pharmacies, and the use of an eyelid speculum, face masks and prophylactic antibiotics. ‘Off-label’ medications prepared by a compounding pharmacy may become contaminated [45, 46]. Eyelid speculums are very commonly used and have traditionally been thought to be very important to reduce the rate of infection [47], but one series of 10,164 injections using an assistant to manually retract the lids, but no speculum, reported only 3 cases of endophthalmitis (0.030%) [28]. There appears to be a long-term trend away from the routine use of prophylactic topical antibiotics, and several large series have reported higher rates of infection in eyes treated with antibiotics than eyes that were not [48–50]. In two small prospective trials using simulated intravitreal injections, bacterial dispersal was significantly reduced by wearing a face mask or by not speaking [51, 52]. One retrospective series of 15,144 injections performed using face masks by the physician and nurse assistant, as well as a drape on the patient’s face, reported zero cases of endophthalmitis [29], but another retrospective series of 15,925 patients reported an incidence of 0.05% despite the use of face masks and povidone-iodine use [30].

Etiology/Pathogenesis

The etiology of infective endophthalmitis is predicted by the clinical features and past history, and this is summarized in table 1 [53–57]. Post-traumatic endophthalmitis is frequently caused by relatively more virulent organisms, such as *Bacillus cereus* [58].

Endogenous endophthalmitis is more frequently caused by fungi, but bacterial cases may also occur [42]. The most common causative organisms include *Candida albicans* and *Aspergillus* species. In bacterial endogenous endophthalmitis, the most common causative organisms are *B. cereus*, *Staphylococcus aureus, Klebsiella*, *Pseudomonas* and *Streptococcus* species [59, 60].

Traditionally, endophthalmitis associated with microbial keratitis has been caused by Gram-negative organisms, *S. aureus*, streptococcal species and various fungi [61]. Outbreaks of *Fusarium* keratitis have been associated with soft contact lenses [62–64], and series of endophthalmitis in eyes with *Fusarium* keratitis have been reported [6, 65].

Infective endophthalmitis following intravitreal injection is frequently due to coagulase-negative staphylococci, although streptococcus isolates have been reported to be significantly more common following intravitreal injection than following cataract surgery [66, 67].

Diagnosis and Ancillary Testing/Differential Diagnosis

Infective endophthalmitis is a clinical diagnosis but may be confirmed by evaluation of intraocular fluid specimens. Its clinical signs are variable and depend on the infecting organism, the duration of infection, the associated inflammation and various patient risk factors, such as prior surgery, trauma and immune status, as previously discussed.

Obtaining intraocular cultures is important in the workup of endophthalmitis. A vitreous specimen is more likely to yield a positive culture result than a simultaneously acquired aqueous specimen [68]. The vitreous specimen can be obtained by needle biopsy (vitreous tap) or by the use of automated vitrectomy instrumentation. If a needle biopsy approach is selected, a butterfly needle may offer better stability than a tuberculin syringe [69]. A single-port transconjunctival sutureless vitrector has been advocated for the treatment of endophthalmitis in the office setting. This device, the Visitrec vitrectomy unit (Insight Instruments, Stuart, FL, USA), combines the theoretical advantages of standard PPV without the associated delays in treatment or increased expenses [70, 71].

Depending on the volume of the specimen and the clinical setting, alternative culture techniques can be selected [1]. The traditional approach, direct inoculation of the specimen onto culture media, is commonly selected. Culture media may include 5% blood agar for the most common bacterial and fungal pathogens; chocolate agar for fastidious organisms such as *Neisseria gonorrhoeae* and *Haemophilus influenzae*; Sabouraud agar for fungi; thioglycollate broth for anaerobes; and anaerobic blood agar. Alternatively, the specimen may be injected into blood culture bottles, which are particularly useful in after-hour emergency cases [72].

The differential diagnosis of marked inflammation following intraocular surgery is listed in table 4. Sterile inflammation may be secondary to retained lens fragments or foreign material introduced during surgery. Retained cortical fragments may cause more severe inflammation than nuclear fragments, and these eyes occasionally present with hypopyon [73].

The toxic anterior-segment syndrome (TASS) is a sterile inflammatory reaction of moderate-to-severe intensity usually within 12–48 h after intraocular surgery. Typical signs include corneal edema, anterior-chamber cell and flare with fibrin and/or hypopyon, an unreactive pupil and elevated intraocular pressure [74]. TASS may be caused by exposure to various foreign substances, including the IOL, ointments and disinfecting compounds [75–77]. In some patients, TASS may be difficult to distinguish from infective endophthalmitis. Typically, TASS presents earlier, and the signs are confined to the anterior segment. The corneal edema may be out of proportion to the level of inflammation. TASS may present in a cluster of patients from the same surgical center.

Eyes with noninfective foreign material in the anterior chamber may appear similar to eyes with endophthalmitis. For example, particles of triamcinolone may migrate anteriorly, mimicking a hypopyon [78]. Intraocular blood, particularly when dehemoglobinized, may be confused with infective material [79, 80].

In addition, intravitreal injections may be associated with sterile intraocular inflammation due to unknown causes [81]. Multiple series have reported culture-negative endophthalmitis occurring in clusters following treatment with a single batch of medication [82–84]. One study concluded that culture-negative inflammation is more common following bevacizumab than ranibizumab [85].

Signs and Symptoms

Ocular Findings

In acute-onset postoperative bacterial endophthalmitis, there is typically acute-onset visual loss and redness, and associations with marked intraocular inflammation, anterior chamber inflammation, fibrin and hypopyon have been reported [1]. Eyelid edema, conjunctival congestion, vitreous inflammation and retinal periphlebitis may be noted. Chronic postoperative endophthalmitis is typically marked by relatively mild but progressive inflammation and an indolent course. In filtering bleb-associated endophthalmitis, clinical features include purulent bleb involvement, as well as aqueous and vitreous inflammation, including hypopyon [3].

Compared with bacterial endophthalmitis, fungal endophthalmitis is generally associated with less inflammation, a more indolent course and less pain. Endogenous endophthalmitis due to *Candida* often manifests as isolated white infiltrates in formed vitreous overlying a localized area of chorioretinitis.

Endophthalmitis following open-globe injuries is often severe and rapidly progressive. In contrast, there is frequently a delay in diagnosis of endophthalmitis associated with microbial keratitis because of the recognition that many cases of keratitis with hypopyon do not have endophthalmitis. Additionally, posterior-segment findings (including echography) may be relatively mild or not helpful in establishing the diagnosis. The diagnosis should be suspected when patients with keratitis continue to worsen despite appropriate topical, systemic and other therapy (including, in some cases, penetrating keratoplasty; fig. 3).

Systemic Findings

Typically, systemic findings in infectious endophthalmitis are minimal. An exception is endogenous endophthalmitis, in which there may be systemic signs of infection, such as fever or debilitation.

Treatment Options

In the management of endophthalmitis, safe and effective antimicrobial agents are selected. In most cases, culture results are not available until days after initiation of treatment. Therefore, initial therapy should provide coverage for a broad range of Gram-positive and -negative organisms. Many of the current treatment guidelines originate from the Endophthalmitis Vitrectomy Study (EVS), a randomized, multicenter, clinical trial which treated all patients with intravitreal vancomycin and amikacin; subconjunctival vancomycin, ceftazidime and dexamethasone; and systemic corticosteroids [86]. The results of the EVS are summarized in table 5 [54, 87, 88]. Several points must be considered when applying these results to clinical practice.

First, the EVS reported a benefit for PPV only in eyes with visual acuity of light perception. However, in selected rapid-onset cases with moderate or severe vitreous inflammation, PPV may be considered, even when visual acuity is better than light perception. PPV may be performed using a two-port (end-irrigating light pipe and vitreous cutter) or standard three-port technique. Small-gauge transconjunctival sutureless vitrectomy is becoming more popular for this indication [89]. An uninvolved crystalline lens may be retained in phakic patients [90].

Second, the EVS only recruited patients with acute-onset endophthalmitis following cataract surgery or secondary IOL implantation. Therefore, these results do not necessarily apply to other forms of endophthalmitis, which are more frequently caused by more virulent organisms. Thus, the benefits of PPV may be more important in these other clinical settings.

Third, the antibiotic choices should be tailored to the individual patient. Even though the EVS used intravitreal amikacin, either intravitreal ceftazidime or ceftriaxone may be considered to avoid the risk of aminoglycoside toxicity. The EVS reported very high rates of antibiotic susceptibility [91], but more recent reports suggest that the rates of antibiotic-resistant organisms may be increasing [92–94]. Although the EVS used subconjunctival antibiotics, two more recent clinical studies showed no difference in outcomes by using subconjunctival antibiotics in addition to intravitreal antibiotics [95, 96]. The EVS reported no benefit from adjunctive systemic amikacin and ceftazidime, but there may be a rationale to use other systemic agents. For example, the fourth-generation fluoroquinolones achieve intraocular drug levels even in the noninflamed eye, although their benefit in endophthalmitis remains unproven [97]. Systemic gatifloxacin (Tequin; Bristol-Myers Squibb, New York, NY, USA) is no longer commercially available because of the associated risks of hypo- and hyperglycemia [98]. Another fourth-generation fluoroquinolone, moxifloxacin (Avelox; Bayer Healthcare, Wuppertal, Germany), is currently available but has the same limitations. Systemic ciprofloxacin may be beneficial for *Pseudomonas*

endophthalmitis, because the MIC_{90} of ciprofloxacin is much lower than that of gatifloxacin or moxifloxacin [99].

Fourth, the EVS treated all patients with systemic corticosteroids. Although systemic corticosteroids may improve final outcomes, caution is advised regarding systemic side effects, particularly in elderly patients and those with diabetes mellitus. As an alternative, especially in bacterial cases, intravitreal dexamethasone (400 micrograms) may be considered [100].

Fifth, the EVS did not recruit patients with suspected fungal endophthalmitis. Many patients with endogenous fungal endophthalmitis will respond to systemic therapy alone, typically in consultation with an internist or infectious disease specialist. Systemic antifungals may be combined with PPV, which reduces fungal load and perhaps increases intraocular penetration of systemic agents. In some patients, intravitreal antifungals are necessary. Traditionally, amphotericin B was commonly used, but some of the newer azole compounds are gaining increased acceptance in many situations. For example, intravitreal voriconazole (VFEND; Pfizer, New York, NY, USA), a synthetic, second-generation triazole, has shown efficacy in some reports [101]. Various antifungal agents are listed in table 6.

Treatment Outcomes and Prognosis

In the EVS, the most important predictor of final visual outcome was presenting visual acuity. Patients with presenting visual acuity of light perception or worse had the poorest outcomes [54]. Thus, early treatment of endophthalmitis is associated with improved visual outcomes. Prompt initiation of therapy is more important than any other factor, including PPV versus vitreous tap or the use of adjunctive systemic antibiotics.

Other independent predictors of poorer visual outcomes in the EVS include older age, diabetes mellitus, corneal infiltrate or ring ulcer, abnormal intraocular pressure, iris neovascularization, an absent red reflex and an open posterior capsule [102]. Certain echographic features, such as dense vitreous opacities, dense vitreous membranes, retinal detachment and choroidal detachment, are associated with a poorer visual prognosis [103, 104].

One large series of patients with endogenous fungal endophthalmitis reported relatively worse outcomes in patients with mold, rather than yeast, infections [105].

Conclusion and Key Points

Infective endophthalmitis is uncommon but may cause severe visual loss, even with prompt diagnosis and appropriate treatment. The clinical presentation aids in categorization of the patient, which helps predict the etiology and causative organisms. Endophthalmitis is a clinical diagnosis, but laboratory confirmation is important. A vitreous sample may be obtained either through needle tap or with automated vitrectomy instrumentation, depending on the clinical situation. Prompt institution of safe and effective antimicrobial therapy is important in achieving best visual outcomes.

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References

1. Doft, B. Focal Points: Modules for Clinicians. San Francisco: American Academy of Ophthalmology; 1997. Endophthalmitis Management.
2. Shirodkar AR, Pathengay A, Flynn HW Jr, et al. Delayed- versus acute-onset endophthalmitis after cataract surgery. Am J Ophthalmol. 2012; 153:391–398. [PubMed: 22030353]
3. Jacobs DJ, Leng T, Flynn HW Jr, et al. Delayed-onset bleb-associated endophthalmitis: presentation and outcome by culture result. Clin Ophthalmol. 2011; 5:739–744. [PubMed: 21691583]
4. Henry CR, Flynn HW Jr, Miller D, et al. Delayed-onset endophthalmitis associated with corneal suture infections. J Ophthalmic Inflamm Infect. 2013; 3:51. [PubMed: 23758694]
5. Ahmed Y, Pathengay A, Flynn HW Jr, Isom R. Delayed-onset endophthalmitis associated with Ex-PRESS mini glaucoma shunt. Ophthalmic Surg Lasers Imaging. 2012; 43:e62–e63. [PubMed: 22785601]
6. Rosenberg KD, Flynn HW Jr, Alfonso EC, et al. *Fusarium* endophthalmitis following keratitis associated with contact lenses. Ophthalmic Surg Lasers Imaging. 2006; 37:310–313. [PubMed: 16898392]
7. Schwartz SG, Flynn HW, Scott IU. Endophthalmitis after intravitreal injections (review). Expert Opin Pharmacother. 2009; 10:2119–2126. [PubMed: 19586422]
8. Lundstrom M, Wejde G, Stenevi U, et al. Endophthalmitis after cataract surgery: a nationwide prospective study evaluating incidence in relation to incision type and location. Ophthalmology. 2007; 114:866–870. [PubMed: 17324467]
9. Patwardhan A, Rao GP, Saha K, et al. Incidence and outcomes evaluation of endophthalmitis management after phacoemulsification and 3-piece silicone intraocular lens implantation over 6 years in a single eye unit. J Cataract Refract Surg. 2006; 32:1018–1021. [PubMed: 16814063]
10. Kamalarajah S, Silvestri G, Sharma N, et al. Surveillance of endophthalmitis following cataract surgery in the UK. Eye (Lond). 2004; 18:580–587. [PubMed: 15184923]
11. Miller JJ, Scott IU, Flynn HW Jr, et al. Acute-onset endophthalmitis after cataract surgery (2000–2004): incidence, clinical settings, and visual acuity outcomes after treatment. Am J Ophthalmol. 2005; 139:983–987. [PubMed: 15953426]
12. Das T, Hussain A, Naduvilath T, et al. Case control analyses of acute endophthalmitis after cataract surgery in South India associated with technique, patient care, and socioeconomic factors. J Ophthalmol. 2012; 2012:298459. [PubMed: 22523647]
13. Eifrig CWG, Flynn HW Jr, Scott IU, et al. Acute-onset postoperative endophthalmitis: review of incidence and visual outcomes (1995–2001). Ophthalmic Surg Lasers. 2002; 33:373–378. [PubMed: 12358290]
14. West ES, Behrens A, McDonnell PJ, et al. The incidence of endophthalmitis after cataract surgery among the U.S. Medicare population increased between 1994 and 2001. Ophthalmology. 2005; 112:1388–1394. [PubMed: 15953637]
15. Govetto A, Virgili G, Menchini F, Lanzetta P, Menchini U. A systematic review of endophthalmitis after microincisional versus 20-gauge vitrectomy. Ophthalmology. 2013; 120:2286–2291. [PubMed: 23769332]
16. Essex RW, Yi Q, Charles PG, et al. Post-traumatic endophthalmitis. Ophthalmology. 2004; 111:2015–2022. [PubMed: 15522366]
17. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med. 2004; 351:2805–2816. [PubMed: 15625332]
18. Heier JS, Antoszyk AN, Pavan PR, et al. Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study. Ophthalmology. 2006; 133:633–642.

19. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006; 355:1432–1444. [PubMed: 17021319]
20. Rosenfeld PR, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006; 355:1419–1431. [PubMed: 17021318]
21. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012; 119:2537–2548. [PubMed: 23084240]
22. Martin DF, Maguire MG, et al. Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012; 119:1388–1398. [PubMed: 22555112]
23. Fung AE, Rosenfeld PJ, Reichel E. The international intravitreal bevacizumab safety survey: using the internet to assess drug safety worldwide. Br J Ophthalmol. 2006; 90:1344–1349. [PubMed: 16854824]
24. Rasmussen A, Bloch SB, Fuchs J, et al. A 4-year longitudinal study of 555 patients treated with ranibizumab for neovascular age-related macular degeneration. Ophthalmology. 2013; 120:2630–2636. [PubMed: 23830760]
25. Gillies MC, Walton R, Simpson JM, et al. Prospective audit of exudative age-related macular degeneration: 12-month outcomes in treatment-naïve eyes. Invest Ophthalmol Vis Sci. 2013; 54:5754–5760. [PubMed: 23821201]
26. Englander M, Chen TC, Paschalis EI, et al. Intravitreal injections at the Massachusetts Eye and Ear Infirmary: analysis of treatment indications and postinjection endophthalmitis rates. Br J Ophthalmol. 2013; 97:460–465. [PubMed: 23390167]
27. Moshfeghi AA, Rosenfeld PJ, Flynn HW Jr, et al. Endophthalmitis after intravitreal vascular [corrected] endothelial growth factor antagonists: a six-year experience at a university referral center. Retina. 2011; 31:662–668. [PubMed: 21836400]
28. Fineman HS, Hsu J, Spirn MJ, Kaiser RS. Bimanual assisted eyelid retraction technique for intravitreal injections. Retina. 2013; 33:1968–1970. [PubMed: 23609121]
29. Shimada H, Hattori T, Mori R, et al. Minimizing the endophthalmitis rate following intravitreal injections using 0. 25% povidoneiodine irrigation and surgical mask. Graefes Arch Clin Exp Ophthalmol. 2013; 251:1885–1890. [PubMed: 23389553]
30. Mithal K, Mathai A, Pathengay A, et al. Endophthalmitis following intravitreal anti-VEGF injections in ambulatory surgical centre facility: incidence, management and outcome. Br J Ophthalmol. 2013; 97:1609–1612.
31. Westfall AC, Osborn A, Kuhl D, et al. Acute endophthalmitis incidence: intravitreal triamcinolone. Arch Ophthalmol. 2005; 123:1075–1077. [PubMed: 16087840]
32. Moshfeghi DM, Kaiser PK, Scott IU, et al. Acute endophthalmitis following intravitreal triamcinolone acetonide injection. Am J Ophthalmol. 2003; 136:791–796. [PubMed: 14597028]
33. Ciulla TA, Starr MB, Masket S. Bacterial endophthalmitis prophylaxis for cataract surgery: an evidence-based update. Ophthalmology. 2002; 109:13–26. [PubMed: 11772573]
34. Wallin T, Parker J, Jin Y, et al. Cohort study of 27 cases of endophthalmitis at a single institution. J Cataract Refract Surg. 2005; 31:735–741. [PubMed: 15899450]
35. Cao H, Zhang L, Li L, Lo S. Risk factors for acute endophthalmitis following cataract surgery: a systematic review and meta-analysis. PLoS One. 2013; 8:e71731. [PubMed: 23990980]
36. Lalwani GA, Flynn HW Jr, Scott IU, et al. Acute-onset endophthalmitis after clear corneal cataract surgery (1996–2005): clinical features, causative organisms, and visual acuity outcomes. Ophthalmology. 2008; 115:473–476. [PubMed: 18067969]
37. Barry P, Seal DV, Gettinby G, et al. ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery: preliminary report of principal results from a European multicenter study. J Cataract Refract Surg. 2006; 32:407–410. [PubMed: 16631047]
38. Behndig A, Cochener B, Guell JL, et al. Endophthalmitis prophylaxis in cataract surgery: overview of current practice patterns in 9 European countries. J Cataract Refract Surg. 2013; 39:1421–1431. [PubMed: 23988244]

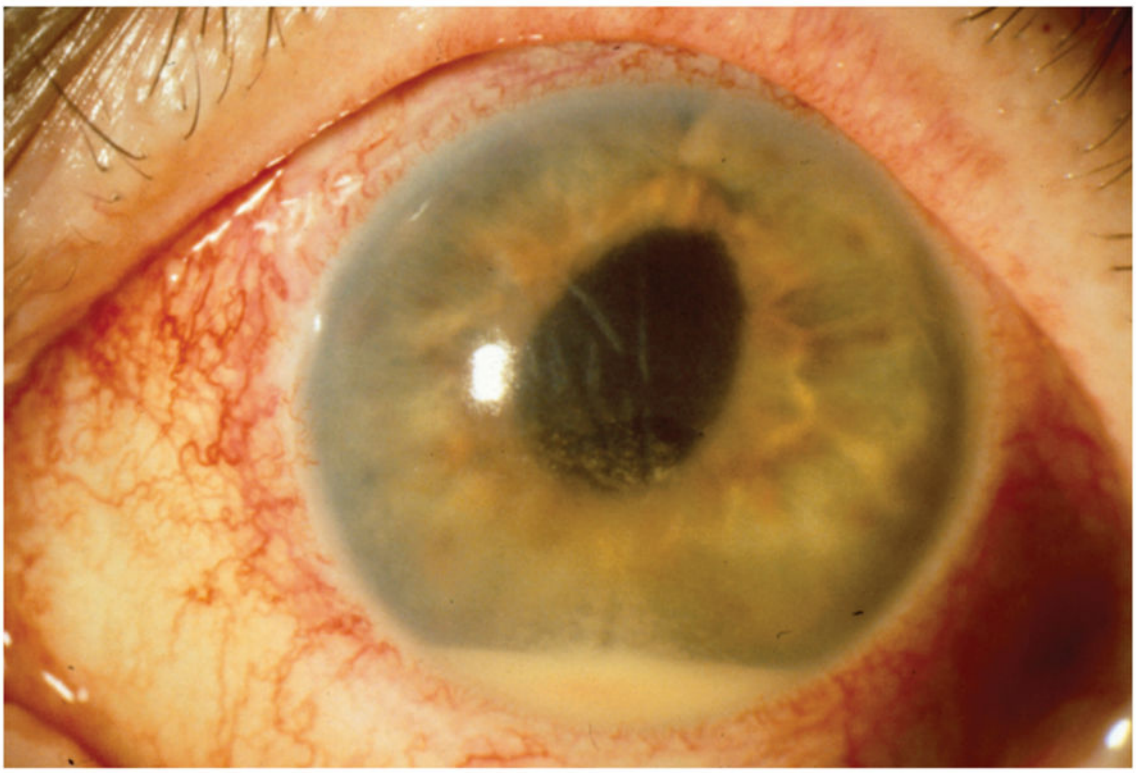
39. Gower EW, Lindsley K, Nanji AA, Leyngold I, McDonnell PJ. Perioperative antibiotics for prevention of acute endophthalmitis after cataract surgery. Cochrane Database Syst Rev. 2013; 7:CD006364.
40. Ahmed Y, Schimel AM, Pathengay A, Colyer MH, Flynn HW Jr. Endophthalmitis following open-globe injuries. Eye (Lond). 2012; 26:212–217. [PubMed: 22134598]
41. Parke DW 3rd, Pathengay A, Flynn HW Jr, Albini T, Schwartz SG. Risk factors for endophthalmitis and retinal detachment with retained intraocular foreign bodies. J Ophthalmol. 2012; 2012:758526. [PubMed: 22619702]
42. Schiedler V, Scott IU, Flynn HW Jr, et al. Culture-proven endogenous endophthalmitis: clinical features and visual acuity outcomes. Am J Ophthalmol. 2004; 137:725–731. [PubMed: 15059712]
43. Aziz HA, Berrocal AM, Sisk RA, et al. Intraocular infections in the neonatal intensive care unit. Clin Ophthalmol. 2012; 6:733–737. [PubMed: 22654500]
44. Henry CR, Flynn HW Jr, Miller D, Forster RK, Alfonso EC. Infectious keratitis progressing to endophthalmitis: a 15-year study of microbiology, associated factors, and clinical outcomes. Ophthalmology. 2012; 119:2443–2449. [PubMed: 22858123]
45. Sheyman AT, Cohen BZ, Friedman AH, Ackert JM. An outbreak of fungal endophthalmitis after intravitreal injection of compounded combined bevacizumab and triamcinolone. JAMA Ophthalmol. 2013; 131:864–849. [PubMed: 23640384]
46. Goldberg RA, Flynn HW Jr, Miller D, Gonzalez S, Isom RF. Streptococcus endophthalmitis outbreak after intravitreal injection of bevacizumab: one-year outcomes and investigative results. Ophthalmology. 2013; 120:1448–1453. [PubMed: 23453511]
47. Scott IU, Flynn HW Jr. Reducing the risk of endophthalmitis following intravitreal injections. Retina. 2007; 27:10–12. [PubMed: 17218909]
48. Falavarjani KG, Modarres M, Hashemi M, et al. Incidence of acute endophthalmitis after intravitreal bevacizumab injection in a single clinical center. Retina. 2013; 33:971–974. [PubMed: 23400076]
49. Cheung CS, Wong AW, Lui A, et al. Incidence of endophthalmitis and use of antibiotic prophylaxis after intravitreal injections. Ophthalmology. 2012; 119:1609–1614. [PubMed: 22480743]
50. Bhavsar AR, Stockdale CR, Ferris FL, et al. Update on risk of endophthalmitis after intravitreal drug injections and potential impact of elimination of topical antibiotics. Arch Ophthalmol. 2012; 130:809–810. [PubMed: 22801859]
51. Wen JC, McCannel CA, Mochon AB, Garner OB. Bacterial dispersal associated with speech in the setting of intravitreous injections. Arch Ophthalmol. 2011; 129:1551–1554. [PubMed: 21825179]
52. Doshi RR, Leng T, Fung AE. Reducing oral flora contamination of intravitreal injections with face mask or silence. Retina. 2012; 32:473–476. [PubMed: 22374155]
53. Bannerman TL, Rhoden DL, McAllister M, et al. The source of coagulase-negative staphylococci in the Endophthlamitis Vitrectomy Study: a comparison of eyelid and intraocular isolates using pulsed-field gel electrophoresis. Arch Ophthalmol. 1997; 115:357–361. [PubMed: 9076208]
54. Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study: a randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Arch Ophthalmol. 1995; 113:1479–1496. [PubMed: 7487614]
55. Clark WL, Kaiser PK, Flynn HW Jr, et al. Treatment strategies and visual acuity outcomes in chronic postoperative *Propionibacterium acnes* endophthalmitis. Ophthalmology. 1999; 106:1665–1670. [PubMed: 10485532]
56. Chaudhry NA, Flynn HW Jr, Smiddy WE, et al. *Xanthomonas maltophilia* endophthalmitis after cataract surgery. Arch Ophthalmol. 2000; 188:572–575.
57. Scott IU, Lieb DF, Flynn HW Jr, et al. Endophthalmitis caused by *Mycobacterium chelonae*: selection of antibiotics and outcomes of treatment. Arch Ophthamol. 2003; 121:573–576.
58. Vahey JB, Flynn HW Jr. Results in the management of *Bacillus* endophthalmitis. Ophthalmic Surg. 1991; 22:681–686. [PubMed: 1792034]
59. Scott IU, Matharoo N, Flynn HW Jr, et al. Endophthalmitis caused by *Klebsiella* species. Am J Ophthalmol. 2004; 138:662–663. [PubMed: 15488803]

60. Miller JJ, Scott IU, Flynn HW Jr, et al. Endophthalmitis caused by *Streptococcus pneumoniae*. Am J Ophthalmol. 2004; 138:231–236. [PubMed: 15289132]
61. Scott IU, Flynn HW Jr, Feuer W, et al. Endophthalmitis associated with microbial keratitis. Ophthalmology. 1996; 103:1864–1870. [PubMed: 8942882]
62. Alfonso EC, Cantu-Dibildox J, Munir WM, et al. Insurgence of *Fusarium* keratitis associated with contact lens wear. Arch Ophthalmol. 2006; 124:941–947. [PubMed: 16769827]
63. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. JAMA. 2006; 296:953–963. [PubMed: 16926355]
64. Iyer SA, Tuli SS, Wagoner RC. Fungal keratitis: emerging trends and treatment outcomes. Eye Contact Lens. 2006; 32:267–271. [PubMed: 17099386]
65. Dursun D, Fernandez V, Miller D, et al. Advanced *Fusarium* keratitis progressing to endophthalmitis. Cornea. 2003; 22:300–303. [PubMed: 12792470]
66. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: causative organisms and possible prevention strategies. Retina. 2011; 31:654–661. [PubMed: 21330939]
67. Chen E, Lin MY, Cox J, Brown DM. Endophthalmitis after intravitreal injection: the importance of viridans streptococci. Retina. 2011; 31:1525–1533. [PubMed: 21878800]
68. Donahue SP, Kowalski RP, Jewart BH, et al. Vitreous cultures in suspected endophthalmitis: biopsy or vitrectomy? Ophthalmology. 1993; 100:452–455. [PubMed: 8479699]
69. Raju B, Das T. Hyderabad Endophthalmitis Research Group. Simple and stable technique of vitreous tap. Retina. 2004; 24:803–805. [PubMed: 15492640]
70. Josephberg RG. Endophthalmitis: the latest in current management. Retina. 2006; 26(suppl 6):S47–S50.
71. Hilton GF, Josephberg RG, Halperin LS, et al. Office-based sutureless transconjunctival pars plana vitrectomy. Retina. 2002; 22:725–732. [PubMed: 12476098]
72. Eser I, Kapran Z, Altan T, et al. The use of blood culture bottles in endophthalmitis. Retina. 2007; 27:971–973. [PubMed: 17891025]
73. Irvine WD, Flynn HW Jr, Murray TG, et al. Retained lens fragments after phacoemulsification manifesting as marked intraocular inflammation with hypopyon. Am J Ophthalmol. 1992; 114:610–614. [PubMed: 1443024]
74. Mamalis N, Edelhauser HF, Dawson DG, et al. Toxic anterior segment syndrome. J Cataract Refract Surg. 2006; 32:324–333. [PubMed: 16565012]
75. Jehan FS, Mamalis N, Spencer TS, et al. Postoperative sterile endophthalmitis (TASS) associated with the MemoryLens. J Cataract Refract Surg. 2000; 26:1773–1777. [PubMed: 11134878]
76. Werner L, Sher JH, Taylor JR, et al. Toxic anterior segment syndrome and possible association with ointment in the anterior chamber following cataract surgery. J Cataract Refract Surg. 2006; 32:227–235. [PubMed: 16564997]
77. Duffy RE, Brown SE, Caldwell KL, et al. An epidemic of corneal destruction caused by plasma gas sterilization. The Toxic Endothelial Cell Destruction Syndrome Investigative Team. Arch Ophthalmol. 2000; 188:1167–1176.
78. Moshfeghi AA, Scott IU, Flynn HW Jr, et al. Pseudohypopyon after intravitreal triamcinolone acetonide injection for cystoid macular edema. Am J Ophthalmol. 2004; 138:489–492. [PubMed: 15364241]
79. Nahas Z, Shienbaum G, Smiddy WE, Flynn HW Jr. Hypopyon and pseudoendophthalmitis 1 month after vitrectomy for retinal detachment with subretinal hemorrhage. Ophthalmic Surg Lasers Imaging Retina. 2013; 44:281–283. [PubMed: 23676232]
80. Schwartz SG, Mieler WF, Holz ER, et al. Intravitreal hemoglobin spherulosis: a rare complication of subretinal hemorrhage. Arch Ophthalmol. 2002; 120:85–87. [PubMed: 11786064]
81. Hahn P, Kim JE, Stinnett S, et al. Aflibercept-related sterile inflammation. Ophthalmology. 2013; 120:1100–1101. [PubMed: 23642742]
82. Yamashiro K, Tsujikawa A, Miyamoto K, et al. Sterile endophthalmitis after intravitreal injection of bevacizumab obtained from a single batch. Retina. 2010; 30:485–490. [PubMed: 19952993]

83. Khan P, Khan L, Mondal P. Cluster endophthalmitis following multiple intravitreal bevacizumab injections from a single use vial. Indian J Opthhalmol. 2013 Epub ahead of print.
84. Entezari M, Ramezani A, Ahmadieh H, Ghasemi H. Batch-related sterile endophthalmitis following intravitreal injection of bevacizumab. Indian J Ophthalmol. 2014; 62:468–471. [PubMed: 23619494]
85. Sharma S, Johnson D, Abouammoh H, Hollands S, Brissette A. Rate of serious adverse effects in a series of bevacizumab and ranibizumab injections. Can J Ophthalmol. 2012; 47:275–279. [PubMed: 22687306]
86. Flynn HW Jr, Scott IU. Legacy of the Endophthalmitis Vitrectomy Study (EVS). Arch Ophthalmol. 2008; 126:559–561. [PubMed: 18413530]
87. Durand M. Microbiologic factors and visual outcome in the Endophthalmitis Vitrectomy Study. Am J Ophthalmol. 1997; 124:127–130. [PubMed: 9222255]
88. Doft DH, Wisniewski SR, Kellsy SF, et al. Diabetes and postoperative endophthalmitis in the Endophthalmitis Vitrectomy Study. Arch Ophthalmol. 2001; 119:650–656. [PubMed: 11346391]
89. Tan CS, Wong HK, Yang FP, et al. Outcome of 23-gauge sutureless transconjunctival vitrectomy for endophthalmitis. Eye. 2008; 22:150–151. [PubMed: 17962826]
90. Townsend J, Pathengay A, Flynn HW Jr, Miller D. Management of endophthalmitis while preserving the uninvolved crystalline lens. Clin Ophthalmol. 2012; 6:453–457. [PubMed: 22536036]
91. Han DP, Wisniewski SR, Wilson LA, et al. Spectrum and susceptibilities of microbiologic isolates in the Endophthalmitis Vitrectomy Study. Am J Ophthalmol. 1996; 122:1–17. [PubMed: 8659579]
92. Khera M, Pathengay A, Jindal A, et al. Vancomycin-resistant Gram-positive bacterial endophthalmitis: epidemiology, treatment options, and outcomes. J Ophthalmic Inflamm Infect. 2013; 3:46. [PubMed: 23607574]
93. Jindal A, Pathengay A, Khera M, et al. Combined ceftazidime and amikacin resistance among Gram-negative isolates in acute-onset postoperative endophthalmitis: prevalence, antimicrobial susceptibilities, and visual acuity outcome. J Ophthalmic Inflamm Infect. 2013; 3:62. [PubMed: 24161048]
94. Bispo PJ, Alfonso EC, Flynn HW, Miller D. Emerging 8-methoxyfluoroquinolone resistance among methicillin-susceptible Staphylococcus epidermidis isolates recovered from patients with endophthalmitis. J Clin Microbiol. 2013; 51:2959–2963. [PubMed: 23824766]
95. Iyer MN, Han DP, Yun HJ, et al. Subconjunctival antibiotics for acute post-cataract extraction endophthalmitis: is it necessary? Am J Ophthalmol. 2004; 137:1120–1121. [PubMed: 15183800]
96. Smiddy WE, Smiddy RJ, Ba'Arath B, et al. Subconjunctival antibiotics in the treatment of endophthalmitis managed without vitrectomy. Retina. 2005; 25:751–758. [PubMed: 16141864]
97. Hariprasad SM, Mieler WF, Holz ER. Vitreous and aqueous penetration of orally administered gatifloxacin in humans. Arch Ophthalmol. 2004; 121:345–350.
98. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med. 2006; 354:1352–1361. [PubMed: 16510739]
99. Duggirala A, Joseph J, Sharma S, et al. Activity of newer fluoroquinolones against Gram-positive and Gram-negative bacteria isolated from ocular infections: an in vitro comparison. Indian J Ophthalmol. 2007; 55:15–19. [PubMed: 17189881]
100. Das T, Jalali S, Gothwal VK, Sharma S, Naduvilath TJ. Intravitreal dexamethasone in exogenous bacterial endophthalmitis: results of a prospective randomised study. Br J Ophthalmol. 1999; 83:1050–1055. [PubMed: 10460774]
101. Breit SM, Hariprasad SM, Mieler WF, et al. Management of endogenous fungal endophthalmitis with voriconazole and caspofungin. Am J Ophthalmol. 2005; 139:135–140. [PubMed: 15652837]
102. Johnson MW, Doft BH, Kelsey SF, et al. The Endophthalmitis Vitrectomy Study: relationship between clinical presentation and microbiologic spectrum. Ophthalmology. 1997; 104:261–272. [PubMed: 9052630]
103. Das T, Kunimoto DY, Sharma S, et al. Relationship between clinical presentation and visual outcome in postoperative and posttraumatic endophthalmitis in south central India. Indian J Ophthalmol. 2005; 53:5–16. [PubMed: 15829741]

104. Rachitskaya AV, Flynn HW Jr, Fisher YL, Ayres B. Correlation between baseline echographic features of endophthalmitis, microbiologic isolates, and visual outcomes. Clin Ophthalmol. 2013; 7:779–785. [PubMed: 23637520]

105. Sridhar J, Flynn HW Jr, Kuriyan AE, Miller D, Albini T. Endogenous fungal endophthalmitis: risk factors, clinical features, and treatment outcomes in mold and yeast infections. J Ophthalmic Inflamm Infect. 2013; 3:60. [PubMed: 24053550]



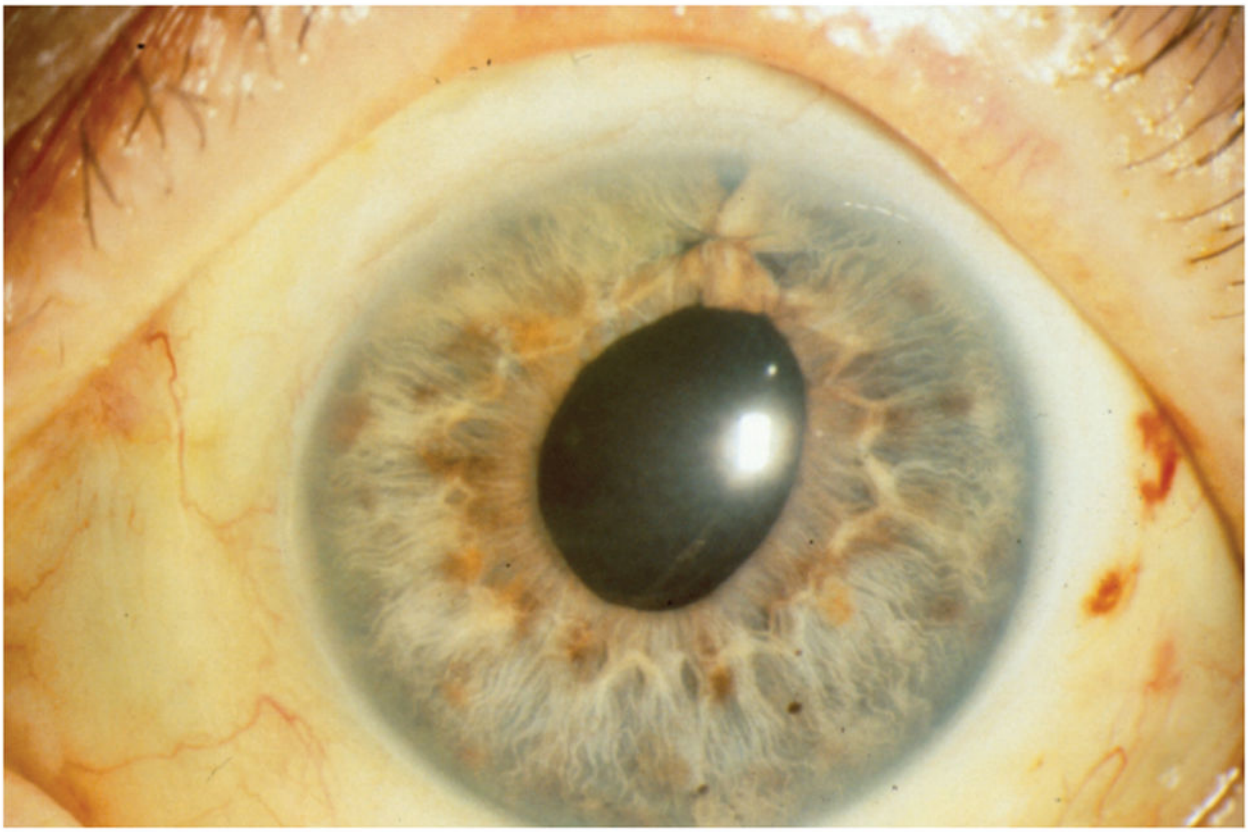


Fig. 1.

a Acute-onset postoperative endophthalmitis. Note conjunctival injection, corneal edema and hypopyon. **b** Resolution of infection following treatment.

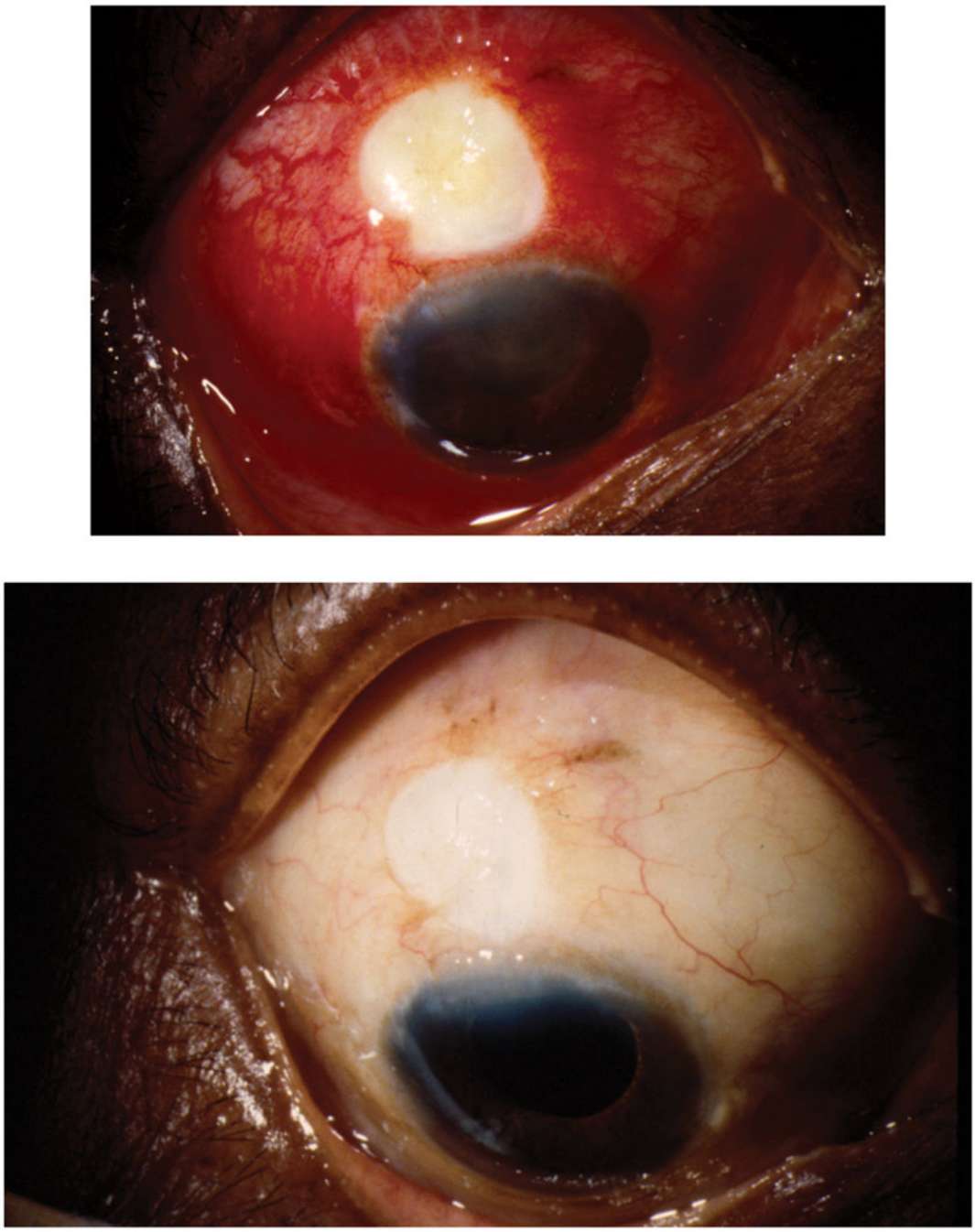


Fig. 2.

a Endophthalmitis associated with filtering bleb. Note conjunctival injection, purulent filtering bleb and anterior chamber fibrin. **b** Resolution of infection following treatment.

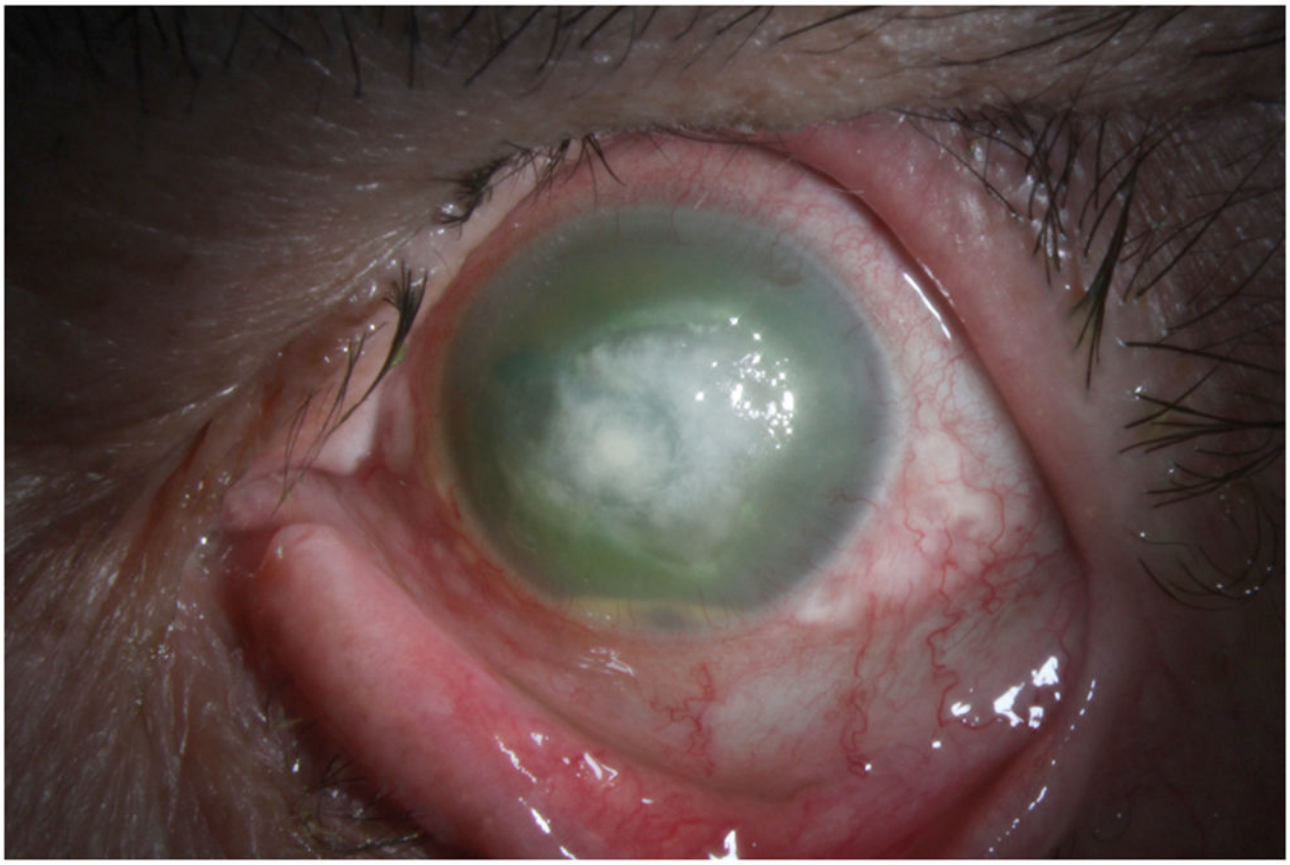


Fig. 3.
Endophthalmitis associated with microbial keratitis.

Table 1

Categories of endophthalmitis with common causative organisms

Category	Common microorganisms		
Acute onset, postoperative	Coagulase-negative Staphylococcus	*Staphylococcus aureus*	*Streptococcus* spp.
Delayed onset (chronic), postoperative	*Propionibacterium acnes*	*Candida parapsilosis*	Coagulase-negative staphylococcus
Filtering bleb associated	*Streptococcus* spp.	*Staphylococcus* spp.	*Haemophilus influenzae*
Posttraumatic	*Staphylococcus* spp.	*Bacillus cereus*	
Endogenous	*Candida albicans*	*Aspergillus* spp.	
Following microbial keratitis	Gram-negative organisms	*Staphyloccocus aureus*	*Fusarium* spp.
Following intravitreal injection	Coagulase-negative Staphylococcus	*Streptococcus viridans*	

Table 2

Incidence of endophthalmitis following intravitreal injection: selected prospective clinical trials

Study	Medication	Cases, n	Treated eyes, n	Incidence, %
VISION [17]	Pegaptanib sodium (Macugen; Valeant, West Laval, Que., Canada)	12[a]	890	1.3
Ranibizumab phase I/II [18]	Ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA)	1	62	1.6
ANCHOR [19]	Ranibizumab	2[b]	277	0.7
MARINA [20]	Ranibizumab	5[c]	477	1.0
VIEW [21]	Ranibizumab	3	595	0.5
	Aflibercept (Eylea; Regeneron, Tarrytown, NY, USA)	3	1,824	0.2
CATT [22]	Ranibizumab	4	599	0.7
	Bevacizumab (Avastin; Genentech)	7	586	1.2[d]

These studies reported the incidence per eye (most eyes received a series of injections).

[a] Two thirds of cases were associated with deviations in the injection protocol.

[b] In the 0.3-mg group, there were 0/137 cases (0%). In the 0.5-mg group, there were 2/140 cases (1.4%). Pooled data are presented here.

[c] In the 0.3-mg group, there were 2/238 cases (0.8%). In the 0.5-mg group, there were 3/239 cases (1.3%). Pooled data are presented here.

[d] Difference not statistically significant.

Table 3

Incidence of endophthalmitis following intravitreal injection: selected observational case series

First author	Medication	Cases, n	Injections, n	Incidence, %
Westfall [31]	Triamcinolone acetonide	1	1,006	0.099
Fung [23]	Bevacizumab	1	7,113	0.014
Rasmussen [24]	Ranibizumab	2	7,584	0.026
Gillies [25]	Ranibizumab and bevacizumab	2	9,162	0.022
Englander [26]	Ranibizumab, bevacizumab, pegaptanib and triamcinolone acetonide	3	10,208	0.029
Moshfeghi [27]	Ranibizumab, bevacizumab and pegaptanib	12	60,322	0.020
Fineman [28]	Bevacizumab and ranibizumab	3	10,164	0.030
Shimada [29]	Ranibizumab, bevacizumab and pegaptanib	0	15,144	0
Mithal [30]	Ranibizumab, bevacizumab and pegaptanib	8	15,925	0.050

These retrospective studies reported incidence rates per injection (not per eye).

Table 4

Differential diagnosis of marked inflammation following cataract surgery

Endophthalmitis
Toxic anterior-segment syndrome (TASS)
Retained lens fragments
Flare-up of preexisting uveitis
Triamcinolone acetonide particles
Long-standing (dehemoglobinized) vitreous hemorrhage

Table 5

Endophthalmitis Vitrectomy Study (EVS)

(1)	Enrollment criteria
	Acute postoperative endophthalmitis (within 6 weeks of surgery)
	Following cataract surgery or secondary to intraocular lens implantation
(2)	Vitreous tap versus pars plana vitrectomy (PPV)
	Patients with presenting visual acuity of hand motions (HM) or better
	No difference in outcomes between vitreous tap and PPV
	Patients with presenting visual acuity of light perception
	Better visual outcomes with PPV than with vitreous tap
	Statistically significant
	Diabetic patients with presenting visual acuity of HM or better
	Slightly better visual outcomes with PPV than with vitreous tap
	Not statistically significant
	Either PPV or vitreous tap could be considered in this situation
(3)	Systemic antibiotics
	Systemic amikacin and ceftazidime offered no additional benefit over the observation group
	Other systemic antibiotics were not evaluated

Table 6

Clinically important antifungal agents

Agent	Mechanism of action
Intravitreal	
Amphotericin B	Disrupts fungal cell membranes
Fluconazole[a]	Inhibits the synthesis of fungal cell membranes
Voriconazole	Inhibits the synthesis of fungal cell membranes
Intravenous	
Amphotericin B	Disrupts fungal cell membranes
Echinocandins	Disrupt fungal cell walls
Fluconazole	Inhibits the synthesis of fungal cell membranes
Voriconazole	Inhibits the synthesis of fungal cell membranes
Oral	
Fluconazole	Inhibits the synthesis of fungal cell membranes
Itraconazole	Inhibits the synthesis of fungal cell membranes
Ketoconazole	Inhibits the synthesis of fungal cell membranes
Posaconazole	Inhibits the synthesis of fungal cell membranes
Voriconazole	Inhibits the synthesis of fungal cell membranes

[a]Experimental.