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REVIEW

Endophthalmitis: state of the art

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Abstract: Endophthalmitis is an uncommon diagnosis but can have devastating visual outcomes. Endophthalmitis may be endogenous or exogenous. Exogenous endophthalmitis is caused by introduction of pathogens through mechanisms such as ocular surgery, open-globe trauma, and intravitreal injections. Endogenous endophthalmitis occurs as a result of hematogenous spread of bacteria or fungi into the eye. These categories of endophthalmitis have different risk factors and causative pathogens, and thus require different diagnostic, prevention, and treatment strategies. Novel diagnostic techniques such as real-time polymerase chain reaction (RT-PCR) have been reported to provide improved diagnostic results over traditional culture techniques and may have a more expanded role in the future. While the role of povidone-iodine in prophylaxis of postoperative endophthalmitis is established, there remains controversy with regard to the effectiveness of other measures, including prophylactic antibiotics. The Endophthalmitis Vitrectomy Study (EVS) has provided us with valuable treatment guidelines. However, these guidelines cannot be directly applied to all categories of endophthalmitis, highlighting the need for continued research into attaining improved treatment outcomes.

Keywords: endophthalmitis, exogenous, endogenous, postoperative, intravitreal injection

Introduction

Endophthalmitis is a rare but potentially sight-threatening disease characterized by marked inflammation of intraocular tissues and fluids.[1] This ocular pathology can be divided into broad categories of exogenous and endogenous endophthalmitis. Exogenous endophthalmitis is caused by inoculation of the eye by microorganisms from the external environment and most commonly occurs as a complication of ocular surgery, trauma, or intravitreal injections.[1] Endogenous endophthalmitis is caused by hematogenous spread of infectious organisms from distant sites of the body. Both categories of endophthalmitis lead to subsequent intraocular inflammation and potentially severe visual loss.[2]

Classification of endophthalmitis

Acute-onset postoperative endophthalmitis

Background and incidence

Acute-onset postoperative endophthalmitis (Figure 1) is generally defined as occurring within 6 weeks of an ocular procedure. Cataract surgeries are responsible for the majority of these cases.[3,4] The reported incidence of acute-onset postoperative endophthalmitis following cataract surgery ranges from 0.03% to 0.2%.[5–12] Less commonly, acute-onset postoperative endophthalmitis has been reported following other ocular procedures including penetrating keratoplasty,[5,13,14] scleral buckling,[15] glaucoma drainage device implantation,[16] and others.

Due to increasing utilization of pars plana vitrectomy (PPV),[17] there is increasing interest in endophthalmitis following this type of surgery. Reported incidence rates

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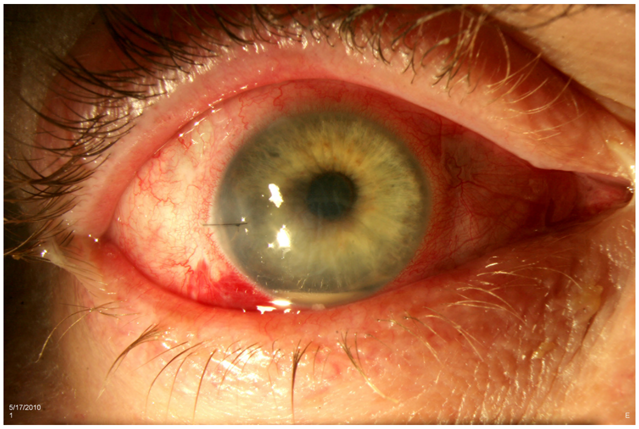

Figure 1 Acute-onset postoperative endophthalmitis (note the sutured corneal wound and hypopyon).

range from 0% to 2.4% for 20 G surgeries (with most rates falling between 0.02% and 0.05%) and 0%–1.3% following 23 G and 25 G PPV.[18–23]

Presentation

In the Endophthalmitis Vitrectomy Study (EVS),[24] 94% of patients with acute-onset postoperative endophthalmitis following cataract surgery or secondary intraocular lens (IOL) implantation presented with decreased visual acuity, 82% with conjuctival injection, 74% with eye pain, and approximately 35% with eyelid edema. Acute-onset postoperative endophthalmitis following other types of surgery present with same general signs, to varying degrees.[22,25]

Risk factors

Among patients undergoing cataract surgery, preoperative risk factors associated with acute-onset postoperative endophthalmitis include blepharitis, diabetes mellitus, and older age.[12,26–30] Perioperative risk factors include preoperative steroids, intraoperative complications, posterior capsular rupture, vitreous loss, and surgeons with less experience.[11,26,27,29–36] Some series have reported clear corneal incisions and lack of intracameral antimicrobials as risk factors but these are controversial. Postoperative risk factors include inpatient status and wound leak on postoperative day 1.[37,38]

Causative organisms

The EVS recruited only patients with suspected bacterial endophthalmitis. The investigators reported that among culture-positive cases, 94.2% of isolates were Gram-positive bacteria.[24] Among these, coagulase-negative staphylococci were the most commonly identified pathogens (70%) followed by *Staphylococcus aureus* (9.9%) and *Streptococcus* species (9%).[24] Coagulase-negative *Staphylococcus* species have also been the predominant isolates reported in endophthalmitis following PPV.[21,22]

There were no reported cases of acute-onset postoperative fungal endophthalmitis in the EVS and other US-based studies.[5,39] However, two publications from India reported a high incidence of postoperative fungal endophthalmitis ranging from 17% to 22%.[40,41]

Delayed-onset postoperative endophthalmitis

Background and incidence

Delayed-onset (chronic) postoperative endophthalmitis (Figure 2) is generally defined as occurring more than 6 weeks after surgery.[42] A recent study reported a mean of 343 days from the date of surgery to the date of diagnosis.[43] Delayed-onset postoperative endophthalmitis is less common than the acute-onset category with a reported ratio of approximately 1:3.5.[43] Similarly, delayed-onset post-cataract endophthalmitis was reported to account for only 7.2% of all postoperative endophthalmitis cases.[3] The incidence of delayed-onset postoperative endophthalmitis has been reported at 0.02%.[44]

Presentation

Delayed-onset postoperative endophthalmitis typically progresses slowly and may involve only mild inflammation.[43] When compared with acute-onset type, delayed-onset postoperative endophthalmitis is less commonly associated with hypopyon. Pain may or may not be present. Characteristic white plaques within the capsular bag are frequently seen.[43]

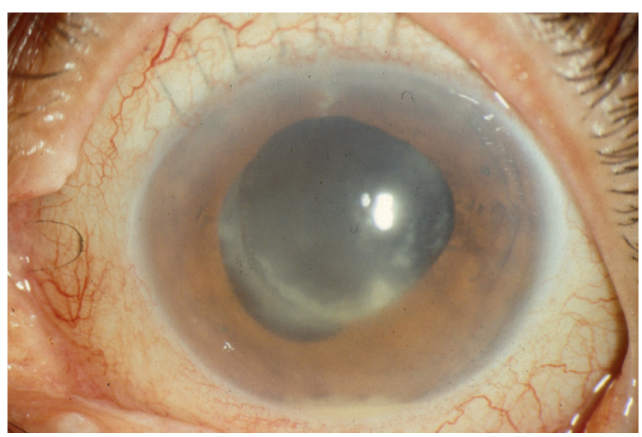

Figure 2 Delayed-onset (chronic) postoperative endophthalmitis (note the small hypopyon and peripheral intracapsular infiltrates).

Causative organisms

Propionibacterium acnes is the most common microorganism isolated in culture-positive cases of chronic postoperative endophthalmitis, accounting for 41%–63% of cases.[43–45] Fungal infections are also important causative pathogens and are responsible for 16%–27% of cases.[43–45]

Bleb-associated endophthalmitis

Background and incidence

Bleb-associated endophthalmitis (Figure 3) may occur following trabeculectomy in either an acute (<4 weeks) or more commonly delayed (>4 weeks) onset.[46] The reported mean time from surgery to diagnosis varies but has generally been in the range of approximately 1.5 years[47] to 7 years[48,49] and even up to 44 years.[50,51] The reported incidence rates of bleb-associated endophthalmitis range from 0.17% to 13.2%.[52–62]

Presentation

Bleb-associated endophthalmitis must be differentiated from blebitis, which presents with a purulent filtering bleb, conjuctival injection and discharge along with photophobia, but no hypopyon or vitreous involvement. Bleb-associated endophthalmitis may be associated with pain, decreased visual acuity, relative afferent pupillary defect, and hypopyon.[50,63] Prodromal symptoms such as headache, browache, and conjunctivitis have been reported in 35% of cases of bleb-associated endophthalmitis.[64]

Risk factors

Reported risk factors include a history of previous blebitis, late-onset bleb leak, younger age, use of antimetabolites, inferior trabeculectomy, thin avascular bleb, axial myopia, blepharitis, and chronic antibiotic use.[62,64–67] While intraoperative use of antimetabolites (specifically mitomycin C) has significantly increased the success rate of trabeculectomies,[68] their use has been associated with a 3-fold increased risk of developing endophthalmitis.[66,69] This increased risk may have been reduced in recent years due to increased surgeons' confidence levels in using intraoperative mitomycin C and a shift from limbus-based to fornix-based conjuctival flaps.[70]

Causative organisms

Similar to acute-onset postoperative endophthalmitis, coagulase-negative staphylococci (specifically *Staphylococcus epidermidis*) and *S. aureus* are the most common isolates in early bleb-associated endophthalmitis.[50,60] In contrast, *Streptococcus* species and gram-negative organisms (specifically *Moraxella catarrhalis*) are the predominant causes of delayed-onset bleb-associated endophthalmitis.[50,71]

Postintravitreal injection endophthalmitis

Background and incidence

The incidence of endophthalmitis following anti-vascular endothelial growth factor (anti-VEGF) injections (Figure 4) has been reported in the range of 0.02%–0.32% per injection.[72] Because most patients are treated with a series of injections, the incidence rate per patient is higher. A large meta-analysis including 350,535 injections among 45 published studies between 2005 and 2012 reported an overall incidence rate of 0.056% or 1 per 1,779 intravitreal injections.[72] The incidence of endophthalmitis following intravitreal injection of triamcinolone acetonide has been reported to be in the range of 0.001%–0.87% per injection, but is generally thought to be higher than that following anti-VEGF injections.[73–75]

Noninfectious endophthalmitis may occur following intravitreal injections. The etiology is poorly understood but may represent an inflammatory reaction to a component in the

Figure 3 Bleb-related endophthalmitis (note the purulent filtering bleb and hypopyon).

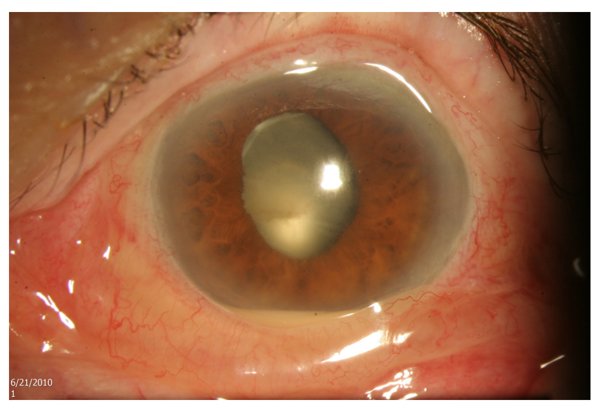

Figure 4 Endophthalmitis following intravitreal injection (note the chemosis and hypopyon).

medication vehicle or migration of triamcinolone acteonide crystals.[76] Reported incidence rates of noninfectious endophthalmitis are 0.37% after aflibercept injections,[77] 0.27%–1.49% after bevacizumab injections,[78–80] and 1.6%–2.7% after triamcinolone acetonide injections.[81,82]

Presentation

Post-intravitreal injection endophthalmitis typically occurs acutely within the first few days.[83,84] Just like other types of endophthalmitis, the most common presenting signs and symptoms of endophthalmitis following intravitreal injections are decreased vision, eye pain, and redness, with presence of anterior chamber cells, hypopyon, and vitritis.[83–86]

Generally, eye pain, anterior chamber fibrin, and profound visual loss are less common in noninfectious postinjection endophthalmitis than in infectious cases and this could potentially help in distinguishing between the two.[76,86] However, in a retrospective review of cases with presumed endophthalmitis, substantial overlap was observed in the presenting signs and symptoms of noninfectious versus infectious types.[83]

Risk factors

Reported risk factors include older age, diabetes mellitus, blepharitis, subconjuctival anesthesia, patient moving/squeezing during the injection, and the use of compounded medications.[87,88] Batch-related noninfectious endophthalmitis has also been reported in 27% and 39% of patients injected from two specific bevacizumab lots.[89]

Causative organisms

Two meta-analyses of isolates from endophthalmitis following intravitreal injection of anti-VEGF agents have reported that overall, coagulase-negative *Staphylococcus* (aggregated mean of 38%–65%) and *Streptococcus* species (29%–31%) are the most cultured organisms.[72,90] Other less common pathogens found are *Bacillus cereus, Enterococcus faecalis, S. epidermidis,* and *S. aureus*. While coagulase-negative *Staphylococcus* species are the most commonly isolated pathogens in both postoperative and postinjection endophthalmitis cases, *Streptococcus* species are 3 times more prevalent in postinjection endophthalmitis than in postoperative cases.[90] Of note, *Streptococcus* species make up 41% of normal oral flora.[91] Therefore, the mechanism of infection in postinjection endophthalmitis may involve contamination of the ocular surface by oropharyngeal bacteria.[90]

In multiple series, a large proportion of clinically suspected endophthalmitis cases were culture-negative (aggregated means of 46.5%–48%).[72,90]

Posttraumatic endophthalmitis

Background and epidemiology

Posttraumatic endophthalmitis is an uncommon but important complication of open-globe injury (Figure 5).[92–94] In recent years, the incidence of endophthalmitis following open-globe trauma has been reported to be between 0% and 12%[95–103] with rates as high as 35% when an intraocular foreign body (IOFB) is present.[94]

Presentation

The presentation and onset of posttraumatic endophthalmitis vary depending on the mechanism of injury and the virulence of organisms involved. Endophthalmitis can present within hours or can be diagnosed years after the initial injury.[104] Signs and symptoms include hypopyon, decreased vision, pain out of proportion to the degree of trauma, retinitis, vitritis, retinal necrosis, and periphlebitis.[96,104] Other findings which could potentially aid the clinician in suspecting endophthalmitis in a case of globe injury include corneal and/or lid edema and loss of red reflex.[105]

Risk factors

Many predisposing factors have been associated with the development of endophthalmitis following open-globe injuries. These include IOFB, traumatic lens rupture, corneal wound, retinal break/detachment, traumatic cataract/posterior lens rupture, dirty wound, long hospital stay, and rural location.[94,95,98,100,101] Delayed wound closure and primary repair (beyond 12–24 hours) have also been reported as important risk factors.[95,96,106,107] Tissue prolapse

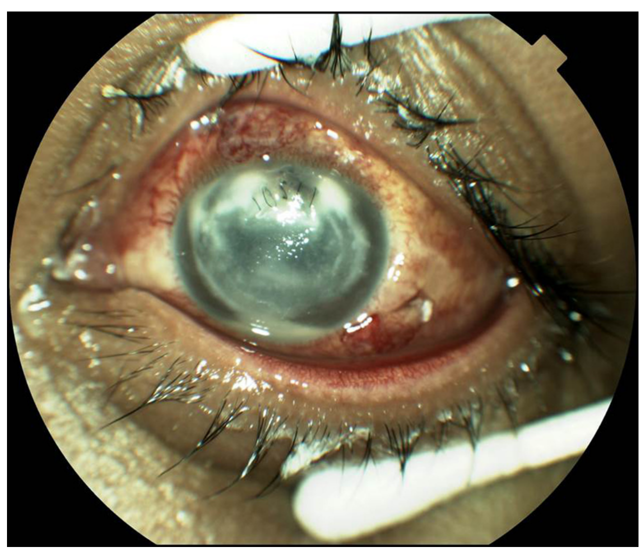

Figure 5 Posttraumatic endophthalmitis (note the sutured corneal wound and hypopyon).

(iris, vitreous) and presence of hyphema may reduce the risk of endophthalmitis since they may act as a barrier against entrance of microbes.[96,100]

Causative organisms

Approximately 80%–90% of culture-positive cases are caused by bacteria.[108,109] Gram-positive cocci are the more common isolates among bacteria, followed by Gram-positive bacilli and other Gram-negative organisms.[108,109] Among Gram-positive cocci, coagulase-negative Staphylococcal organisms (ie, *S. epidermidis* and *Staphyloccoccus saprophyticus*) along with *Streptococcus* species are the predominant groups. Gram-positive *Bacillus* species have been commonly reported in culture isolates of posttraumatic endophthalmitis.[95,101,108–110] *Enterobacter* and *Pseudonomas* species are the most common Gram-negative pathogens and *Aspergillus* species are the most prevalent fungal cause of posttraumatic endophthalmitis.[108,109]

Endogenous endophthalmitis

Background and incidence

In contrast to exogenous endophthalmitis, endogenous endophthalmitis is caused by inoculation of the eye by infectious pathogens spread systemically through the bloodstream and across the blood-ocular barrier.[111] Endogenous endophthalmitis is uncommon and generally accounts for 2%–16% of all reported endophthalmitis cases [92,93,112–114] but the prevalence has been reported to be as high as 41% in one series.[115]

Presentation

Symptoms of endogenous endophthalmitis include decreased vision, eye pain, eye redness, photophobia, floaters, and eyelid swelling.[116–120] Reported ocular signs include hypopyon, subconjuctival hemorrhage, conjuctival injection, iritis/retinitis, corneal edema, anterior chamber cells, and reduced or absent red reflex.[117,119,121]

Since the pathogenesis of endogenous endophthalmitis typically involves hematogenous spread of infection to the eye, systemic findings and bilateral involvement are relatively common. Systemic finding would be signs and symptoms associated with sepsis or bacteremia such as fever, chills, and nausea and vomiting. Bilateral involvement of endogenous endophthalmitis has been reported in 19%–33% of cases.[116–118,120,122]

Risk factors

Several studies have reported a high prevalence of comorbidities, which can potentially predispose patients to development of endogenous endophthalmitis. These include immunocompromisation, diabetes mellitus, malignancies, intravenous drug use, organ abscess, immunosuppressive therapy, indwelling catheter, urinary tract infection, organ transplant, end-stage renal or liver disease, and endocarditis.[116,118,123–125] While most studies evaluating patients with endogenous endophthalmitis have reported predisposing comorbidities, one series reported seven cases of culture proven endogenous endophthalmitis in healthy, immunocompetent individuals without any apparent extraocular loci of infection.[126]

Causative organisms

The pathogens involved in endogenous endophthalmitis vary from study to study and appear to be potentially affected by geographic location and by the origin of the extraocular loci of infection. In contrast to other types of endophthalmitis where bacteria are the most prevalent pathogens, fungal causes were the most commonly isolated microorganisms in several series of endogenous endophthalmitis.[120,122,124,127,128] The leading cause of fungal endogenous endophthalmitis is *Candida albicans*, followed by *Aspergillus* species.[117,118,120,127,128]

Bacterial endogenous endophthalmitis is typically due to Gram-positive species in western nations.[119,120,123,128] Meanwhile, Gram-negative species (specifically *Klebsiella* species) are the main cause of bacterial endogenous endophthalmitis in East Asian countries.[111,116,121,129]

Diagnosis of endophthalmitis

Background

Endophthalmitis is initially suspected based upon clinical presentation, subsequently confirmed with laboratory testing of vitreous or aqueous. It is important to consider potential mimickers of endophthalmitis, including noninfectious inflammation (including toxic anterior segment syndrome), retained lens material, vitreous hemorrhage, and others. While suspected cases of endophthalmitis are typically treated with empiric broad-spectrum antibiotics, identifying the causative microorganisms becomes important in assessing antibiotic susceptibility and also in guiding treatment in cases that do not respond to initial therapy.

Vitreous specimens provide more accurate and reliable culture results than do aqueous cultures.[130–133] For example, in one series, 48% of the cases that had a negative aqueous culture showed microbial growth in vitreous cultures.[134] Vitreous specimens have been traditionally obtained by vitreous tap using a needle and syringe. Other options include using vitrectomy cutters (when PPV is indicated) and office-based automated vitrectors.[135,136] No difference has been shown in the positivity of cultures obtained from vitreous tap versus PPV.[133]

Challenges in diagnosing specific classes of endophthalmitis

Approximately 70% of cases of postoperative endophthalmitis yield a positive culture,[5,11,134] although noninfectious endophthalmitis is relatively more common after intravitreal injection. In a meta-analysis, over 50% of endophthalmitis cases following anti-VEGF injections were culture-negative.[72]

The diagnosis of posttraumatic endopthalmitis may be challenging as the signs and symptoms of endophthalmitis may overlap with those of the initial injury. As such, the presence of hypopyon, vitritis, and/or worsening pain should be considered possible signs of infection.[110,137] Another important diagnostic step in posttraumatic endophthalmitis is the use of imaging techniques to identify the presence of occult IOFBs. In one series, IOFB was identified by clinical examination in 46% of cases, by B-scan echography in 52%, and by computed tomography (CT) in 95%.[138] Magnetic resonance imaging (MRI) may be considered after CT scan (so that metallic IOFBs are ruled out) to better identify non-metallic IOFBs.[139]

In endogenous endophthalmitis, the diagnosis can sometimes be aided by the presence of systemic signs and symptoms of infection and also by blood cultures. However, endogenous endophthalmitis may occur in patients with no overt signs of systemic infection.[126] In addition, negative blood cultures do not necessarily rule out a diagnosis of endogenous endophthalmitis. In one series, blood cultures were positive in only 33% of cases while vitreous samples were positive in 87% of the same patients.[128]

Recent advances in identifying pathogens

Beyond the use of traditional culture media, there have been recent advances in the rapid and accurate detection of causative bacteria and fungi in endophthalmitis.[140] Real-time-polymerase chain reaction (RT-PCR) has been utilized to identify both bacteria[141,142] and fungi.[143,144] As an example, in one series the rate of detection of bacteria in aqueous and vitreous samples increased from approximately 48% to over 95% using PCR.[142] Other novel microbial detection techniques which could potentially be used in rapid diagnosis of endophthalmitis causes are Matrix-Assisted Laser Desorption Ionization–Time of Flight (MALDI-TOF) Mass Spectrometry[145,146] and the use of magneto-DNA nanoparticle system. The latter technique was reported to simultaneously identify 13 species of bacteria in under 2 hours.[147]

Treatment of endophthalmitis

Acute-onset postoperative endophthalmitis

The EVS enrolled patients with endophthalmitis following cataract surgery or secondary IOL implantation within 6 weeks of surgery. The EVS reported that in patients with visual acuity of light perception (LP), when compared to tap and inject, prompt PPV was associated with a 3-fold increase in the proportion of patients achieving visual acuity of 20/40 or better, a 2-fold increase in the proportion of patients achieving visual acuity of 20/100 or better, and a decrease in the proportion of patients achieving visual acuity of worse than 5/200. In patients with better than LP initial visual acuity, however, tap and inject had comparable outcomes as PPV.[24] Based on these results, PPV is generally recommended in patients presenting with LP, and tap and inject is generally recommended for eyes presenting with visual acuity of better than LP.

The role of systemic antibiotics in the treatment of exogenous endophthalmitis remains controversial. The EVS reported that systemic amikacin and ceftazidime had no effect on the final visual outcome.[24] Fourth-generation fluoroquionolones, which were not tested by the EVS, achieve therapeutic levels from the systemic circulation in the noninflamed eye.[148] One study compared the use of oral ciprofloxacin versus moxifloxacin in patients with acute-onset postoperative endophthalmitis and reported that the group treated with oral moxifloxacin had a faster resolution of hypopyon and a decreased need for repeat intravitreal antibiotics.[149]

Delayed-onset postoperative endophthalmitis

The treatment of delayed-onset (chronic) postoperative endophthalmitis is controversial because of the variable clinical presentations and different virulences of the causative organisms. Treatment with PPV combined with partial capsulectomy and injection of intraocular antibiotics led to complete resolution in only 50% of the cases in one series.[150] In another series, recurrent disease occurred in more than 70% of the cases of treated delayed-onset endophthalmitis but when PPV with total capsulectomy and IOL exchange or removal were performed, 90% had complete resolution of endophthalmitis.[43] As a result, total capsulectomy and removal of IOL may be considered for recurrent cases.[43,151]

Postintravitreal injection endophthalmitis

To date, there are no randomized clinical trials regarding the treatment of postinjection endophthalmitis. Since the most common isolates in both acute postoperative and postinjection endophthalmitis are *Staphylococcus* species, many clinicians use the EVS as a guideline for endophthalmitis following intravitreal injections. The role of initial PPV, however, remains unclear in postinjection endophthalmitis. In one series, 90% of the patients treated with tap and inject regained their preinjection visual acuity, while only 46% for patients treated with initial PPV did so.[152]

Bleb-associated endophthalmitis

Streptococcus species and other virulent organisms are relatively more common in bleb-associated endophthalmitis, potentially leading to worse visual outcomes.[46,71] As a result, more aggressive management, including prompt PPV, has been suggested for the treatment of bleb-associated endophthalmitis.[153,154,47,63] Alternatively, another study reported that the eyes that underwent initial PPV had worse outcomes, so this question remains unsettled.[71]

Endogenous endophthalmitis

Management of endogenous endophthalmitis includes a variable combination of systemic and intravitreal antibiotics (or antifungals) and PPV.[155] In a meta-analysis of endogenous endophthalmitis cases published from 2001 to 2012, 56% of the cases received systemic antibiotics, 76% received intravitreal antibiotics (vancomycin most commonly), 12% received intravitreal corticosteroids, and 32% of the eyes underwent PPV.[119] Systemic antibiotics and antifungals (depending on the causative organism) are generally recommended as endogenous endophthalmitis generally has extraocular loci of infection. In a meta-analysis of cases from 1986 to 2012, eyes which underwent PPV were more likely to have a final visual acuity of at least 20/200 and were less likely to progress to enucleation.[119]

Posttraumatic endophthalmitis

While it is generally agreed that primary closure of an open-globe injury is important, there is no consensus with regards to managing established or suspected posttraumatic endophthalmitis. Similar to bleb-associated endophthalmitis, causative organisms in posttraumatic endophthalmitis are generally more virulent. The high prevalence of *Streptococcus* and *Bacillus* species has led to the suggestion of aggressive treatment, including initial PPV when feasible.[105,110,154] In addition to PPV, a combination of intravitreal, subconjuctival, topical, and systemic antibiotics are also recommended.[105,110,156]

Changing trends in microbial profiles and antibiotic susceptibilities

Causative organisms evolve over time. For example, cases of fungal endophthalmitis following intravitreal injections were initially very rare but recently there have been reports of these cases in association with compounded triamcinolone acetonide[157] and compounded bevacizumab.[158]

Two studies have reported that overall, *S.epidermidis* is the predominant pathogen in cases of endophthalmitis followed by *Streptococcus viridans* and other coagulase negative *Staphylococcus* species.[3,159] Vancomycin for Gram-positive bacteria, ceftazidime for Gram-negative bacteria, and voriconazole for fungal endophthalmitis continue to be effective choices for initial treatment of endophthalmitis.[3,159,160]

Visual outcomes of endophthalmitis treatment

Acute-onset postoperative endophthalmitis

In the EVS, only 53% of patients had a final visual acuity of 20/40 or better and 15% had a final visual acuity of 20/200 or worse.[24] In a more recent single-center series, 50% of eyes with acute-onset postoperative endophthalmitis had a final visual acuity of 20/40 or better and overall more than 36% had a final visual acuity of worse than 20/200.[5] A large retrospective study reported that eyes with final visual acuity of 20/40 or better were more likely to be culture-negative or culture-positive for coagulase-negative *Staphylococci*.[11] In another series, coagulase-negative *Staphylococcus* was associated with good final visual outcomes (20/40 or better) while *Streptococcus* species were more prevalent in eyes with worse than 20/200 outcomes.[161]

Delayed-onset postoperative endophthalmitis

Delayed-onset endophthalmitis has been reported to have generally more favorable final visual outcomes when compared to acute-onset cases: 50% achieved final vision of better than 20/40 versus 27% respectively.[43] A review of 4 case series of delayed-onset endophthalmitis reported that eyes infected with *P. acnes* generally had a better final visual outcome while fungal cases were associated with significantly worse outcomes where more than one-fifth of these cases resulted in final visual acuity of worse than 20/200.[162]

Bleb-associated endophthalmitis

Bleb-associated endophthalmits is also associated with unfavorable final visual outcomes due to high prevalence of virulent pathogens such as *Streptococcus* species and Gram-negative bacteria.[46,71] In one series, 35% of cases had a final visual outcome of no light perception (NLP) and in another study this number was 23%.[47,163] Initial visual acuity was reported to have a significant correlation with final visual acuity.[163] In one study, 83% of patients with initial visual acuity of better than LP had a final visual acuity of better than 20/40 while this degree of improvement was achieved by only 31% of patients who presented with LP on initial presentation.[46] Culture positivity with more virulent organisms (such as *Streptococcus* species) was also correlated with worse visual outcomes.[46,163]

Posttraumatic endophthalmitis

Posttraumatic endophthalmitis is associated with generally poor outcomes. One series reported a final visual outcome of NLP in 23% of cases with 45% of cases with hand motions (HM) or worse.[102] Recent studies have reported that a final visual acuity of 20/40 or better was achieved in only 15%–40% of cases with posttraumatic endophthalmitis.[95,98,164,165] One series reported that a good final visual outcome (defined as 20/45 or better) was significantly associated with initial visual acuity of at least LP and an absence of a pupillary fibrin membrane.[165]

Endogenous endophthalmitis

A meta-analysis reported that among endogenous endophthalmitis case series between 2001 and 2012 (a total of 89 eyes), 41% had a final visual acuity of at least 20/200 and 19% underwent enucleation or evisceration. These visual outcomes were improved compared to cases treated prior to 2001, in which final visual acuity of at least 20/200 was seen in only 31%.[119] Among the three broad categories of pathogens found in endogenous endophthalmitis (bacterial, yeast, and molds), cases caused by molds (*Aspergillus* species) are associated with the worst final visual outcomes and cases caused by yeasts (*Candidia* species) with the best. In one study, despite appropriate therapy, 25% of cases of endogenous endophthalmitis caused by *Aspergillus* species required enucleation while there were no enucleated cases with *Candida* isolates.[155] In other studies cases caused by *Aspergillus* were associated with poorer final visual outcomes.[120] In another series, while 80% of cases caused by *Candidia* had a final visual acuity of at least 20/200, only 18% of cases with Gram-positive bacteria achieved that visual acuity.[128]

Postintravitreal injection endophthalmitis

Endophthalmitis cases following intravitreal injections have a high prevalence of more virulent *Streptococcus* species – approximately 3 times more prevalent than in postoperative cases – resulting in relatively poorer visual outcomes.[166] In one series, 80% of the postinjection endophthalmitis cases caused by *Streptococcus* species had final visual outcome of HM or worse.[84] Visual outcomes have varied among studies with the proportion of eyes returning to preinjection visual acuity in three recent studies ranging from 33% to 78%.[84,167,168] Another study concluded that compared to postoperative endophthalmitis, postinjection endophthalmitis was 6 times more likely to have final visual acuity of count fingers (CF) or worse and was much less likely to have improvement in visual acuity following treatment.[166]

Prophylaxis of endophthalmitis

Postoperative endophthalmitis

Endophthalmitis probably cannot be completely prevented, but its incidence may be reduced. The use of preoperative povidone-iodine antisepsis significantly reduces the rate of bacterial endophthalmitis.[169] The European Society of Cataract and Refractive Surgeons (ESCRS) performed a large prospective randomized clinical trial, and reported that intracameral cefuroxime during phacoemulsification reduced the incidence of postoperative endophthalmitis by approximately 5-fold.[29] These results were replicated in later studies originating from different countries,[170–174] although these results remain controversial and intracameral antibiotics are not universally employed even in Europe.

Multiple concerns have been raised about the use of prophylactic intracameral antibiotics. In the US, cefuroxime is not available in prepackaged form and must be reconstituted from powder in the operating room, creating risks of dilution errors and contamination. In addition, prophylactic use of antibiotics increases costs and contributes to increasing bacterial drug resistance.[175]

Similarly, the prophylactic role of topical antibiotics in postoperative endophthalmitis is unclear. While a 2007 survey from American Society of Cataract and Refractive Surgery (ASCRS) members reported that 88% of respondents used preoperative, 91% used perioperative, and 98% used postoperative topical antibiotics,[176] no large-scale prospective studies have been performed to assess their efficacy. Preoperative topical antibiotics significantly reduce conjuctival flora[177] but it is unclear whether this actually decreases the rate of postoperative endophthalmitis. One series reported that substituting a combination of postoperative topical antibiotics and corticosteroids with topical corticosteroids alone did not change the incidence of endophthalmitis.[178]

Postintravitreal injection endophthalmitis

An expert panel has recently reported updated guidelines for reducing the rate of endophthalmitis after intravitreal injections.[179] As with postoperative endophthalmitis, povidone-iodine is effective in reducing endophthalmitis rates following intravitreal injections.[180] Oral flora, including *Streptococcus* species, are more commonly isolated from postinjection cases than from postoperative cases.[90] The routine use of surgical masks during intravitreal injections is logical[181] but has not been reported to reduce endophthalmitis rates.[182] The use of lid speculums has been traditionally recommended as part of a sterile protocol for administrating intravitreal injections.[74,183] However, one series reported omitting lid speculums did not increase the rate of postinjection endophthalmitis.[167]

Numerous studies have reported that prophylactic antibiotics do not reduce the incidence of postintravitreal injection endophthalmitis.[184,185] Furthermore, a meta-analysis of seven studies and 72,823 intravitreal injections found no statistically significant benefit in using postinjection antibiotics.[186] Some series have reported that the use of topical antibiotics immediately after or for 5 days after injections were actually associated with higher rates of postinjection endophthalmitis, perhaps by altering conjunctival flora.[187] In addition, several studies have reported that the use of prophylactic antibiotics for intravitreal injections contributes to emergence of antibiotic-resistant bacteria.[188,189] It has been suggested that prophylactic antibiotics are not a necessary part of intravitreal injection preparation and management.[129]

Posttraumatic endophthalmitis

Antibiotic prophylaxis in posttraumatic endophthalmitis is controversial because there have been very few randomized clinical trials evaluating their effects. Systemic antibiotics have been widely utilized in open-globe injuries[190] and non-use of systemic antibiotics appears to be a risk factor for posttraumatic endophthalmitis.[191,192] In a prospective, randomized study assessing the prophylactic effects of intracameral and intravitreal antibiotics in posttraumatic endophthalmitis, there was a statistically significant reduction in rates of endophthalmitis in antibiotic-treated eyes with IOFB.[193]

Bleb-associated endophthalmitis

There is little or no evidence that prophylactic topical antibiotics prevent bleb-associated endophthalmitis. On the contrary, it was reported that intermittent use or chronic use of antibiotics was associated with an increased risk of bleb-associated endophthalmitis.[66] Risk reduction of bleb-associated endophthalmitis should include addressing its risk factors such as early treatment of blebitis[194] and repair of leaking blebs.[195]

Conclusion

Endophthalmitis remains an important complication of surgery, injections, and trauma. The EVS provided important guidelines which remain relevant to this date.[196] However, those guidelines were derived from cases of acute-onset postoperative endophthalmitis following cataract surgery and secondary IOL implantation and cannot be directly applied to other categories of endophthalmitis. Although it appears unlikely that large-scale randomized clinical trials will be performed on these other categories of endophthalmitis, management strategies continue to evolve by consensus and based on published clinical series.

Accurate identification of causative organisms of endophthalmitis is important, especially in patients who fail to respond to initial broad-spectrum therapy. Newer diagnostic techniques such as RT-PCR may provide more accurate and more sensitive results than traditional culture methods, although at the present time these techniques are not widely available outside of major medical centers.

The types of pathogens involved in infectious endophthalmitis and their antibiotic susceptibilities evolve over time, requiring periodic reassessment. At the present time, almost all isolates are susceptible to the combination of vancomycin and ceftazidime.[159,160] As we continue to collect clinical trial data, treatment of endophthalmitis should continue to improve.

Disclosure

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