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REVIEW

Endophthalmitis: Pathogenesis, clinical presentation, management, and perspectives

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Abstract: Endophthalmitis is a rare but sight-threatening complication that can occur after ocular surgery or trauma or as a consequence of systemic infection. To optimize visual outcome, early diagnosis and treatment are essential. Over recent decades, advances in hygienic standards, improved microbiologic and surgical techniques, development of powerful antimicrobial drugs, and the introduction of intravitreal antibiotic therapy have led to a decreased incidence and improved management of endophthalmitis. However, endophthalmitis still represents a serious clinical problem. This review focuses on current principles and techniques for evaluation and treatment of endophthalmitis. In addition, it addresses recent developments regarding antimicrobial treatment and prophylaxis of infectious endophthalmitis.

Keywords: endophthalmitis, intravitreal, antibiotics, victrectomy, moxifloxacin, voriconazole, caspofungin

Introduction

Endophthalmitis is one of the most devastating diagnoses in ophthalmology. It is a serious intraocular inflammatory disorder affecting the vitreous cavity that can result from exogenous or endogenous spread of infecting organisms into the eye.[1] With any breaching of the ocular bulbus, the potential exists for introducing an infectious inoculum large enough to cause an intraocular infection. This is most commonly seen after intraocular surgery but can also occur as a complication of penetrating ocular trauma or from the adjacent periocular tissues.

Endogenous endophthalmitis is less common and occurs secondary to hematogenous dissemination and spread from a distant infective source in the body. In patients with endogenous endophthalmitis, predisposing risk factors usually exist.[2–6]

In most cases, independent of its origin, the presentation of endophthalmitis consists of reduced or blurred vision, red eye, pain, and lid swelling.[3,5,7,8] Progressive vitritis is one of the key findings in any form of endophthalmitis, and in nearly 75% of patients a hypopyon can be seen at the time of presentation[1] (see Figure 1). Progression of the disease may lead to panophthalmitis, corneal infiltration, and perforation, affection of orbital stuctures, and phthisis bulbi.

In general, the incidence of endophthalmitis has decreased in recent decades[9] and, fortunately, endophthalmitis is rare.[7,9,10] Nonetheless, its evident severity and indistinct prognosis require timely and effective treatment to provide satisfactory visual results.

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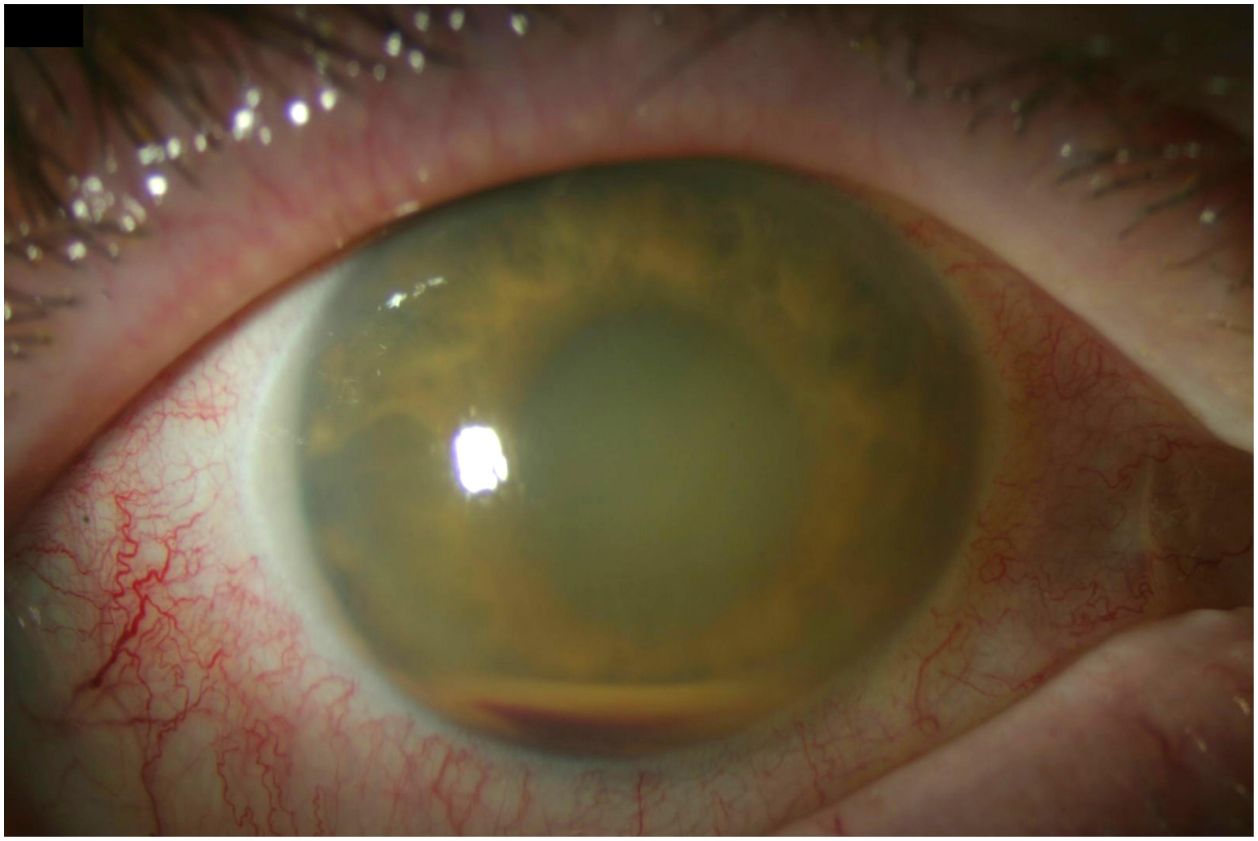

Figure 1 Anterior chamber inflammation, mild corneal edema, and hypopyon in bacterial endophthalmitis.

Pathogenesis and clinical presentation

Exogenous endophthalmitis

Postoperative endophthalmitis

Endophthalmitis after ocular surgery is the most common form of the condition. Cataract surgery is by far the most frequently performed intraocular surgery.[11] Approximately 90% of postoperative endophthalmitis cases develop after this procedure[7,9,10] with an incidence following such surgery ranging from 0.08% to 0.7%.[10,12–15] A recently published meta-analysis indicates that the endophthalmitis rate seems to have increased during the last two decades.[16] According to these data, the rate of endophthalmitis following cataract surgery was about 0.09% during the 1990s and 0.27% in 2000.[16] Greater use of clear corneal incision has been debated as a potential reason for this. Experimental data indicate that with this technique wound architecture seems to be less stable, thus allowing fluctuations in the intraocular pressure and potentially easier entry of bacteria through a less completely sealed wound. Some studies found a three- to four-fold risk for endophthalmitis after clear cornea cataract surgery compared with scleral tunnel incisions.[17,18] In contrast, Lalwani et al reviewed 73 endophthalmitis cases after clear cornea cataract surgery and compared them with the data from the Endophthalmitis Vitrectomy Study (EVS), in which scleral tunnel and clear cornea incisions were used. They found that time to endophthalmitis diagnosis was longer in clear cornea cataract surgery cases but clinical features, causative organisms, and visual acuity outcomes were similar to those reported in the EVS.[19]

Wound integrity also seems to be an important feature influencing the risk for developing endophthalmitis in pars plana vitrectomy. In general, the incidence of endophthalmitis after pars plana vitrectomy is low (0.03%–0.05%).[10,20] Nevertheless, recent data indicate that the use of sutureless small incision techniques (eg, 23- or 25-gauge incision size) is significantly associated with a higher rate of postoperative endophthalmitis than the sutured 20-gauge technique.[21]

However, endophthalmitis can also complicate other ocular surgeries and procedures such as intravitreal injections.[22,23] Some data suggest that penetrating keratoplasty, trabeculectomy, and glaucoma drainage device implantation have a higher risk of being complicated by endophthalmitis than cataract surgery.[24–26] Regarding glaucoma filtering surgery,

endophthalmitis is reported to occur after 0.2%–9.6% of trabeculectomies,[24,27–32] and its incidence seems to increase with the rising use of antifibrotic agents, such as mitomycin-C or 5-fluorouracil.[27–29,32,33] Endophthalmitis rarely occurs after external ocular surgeries including scleral buckling, pterygium excision, removal of corneal sutures, and strabological interventions.[34–38]

In general, secondary intraocular lens placement seems to be associated with the highest risk for developing endophthalmitis (0.2%–0.37%) and pars plana vitrectomy with the lowest (0.03%–0.05%).[10,20]

Preoperative risk factors include eyelid abnormalities, blepharitis, conjunctivitis, cannuliculitis, lacrimal duct obstructions, contact lens wear, and ocular prosthesis in the fellow orbit.[39–42]

The ocular surface and the adnexa are considered the primary sources of infection in postoperative endophthalmitis.[41] However, contaminated agents or surgical equipment used perioperatively may also be a source of infection.[43–45] In addition, perioperative variations seem to have some impact on postoperative endophthalmitis rate; different intraocular lens (IOL) materials potentially act as vectors for bacterial spread into the eye[11,46,47] and viscoelastic substances, such as sodium hyaluronate, or hydroxypropylmethylcellulose may facilitate transmission of bacteria to the eye.[48,49]

Knowledge about the cause of endophthalmitis is essential because the spectrum of organisms may change, warranting different therapeutic approaches. Bacteria infections are the most common cause of postoperative endophthalmitis, and Gram-positive isolates account for most cases.[7,10,15,50] Fungal infections may also occur, particularly in association with the use of contaminated ocular irrigation fluids.[43,51]

Postoperative endophthalmitis can be either sterile or infectious. In the EVS, only 69.3% of cases met the criteria for laboratory-confirmed infection.[7] The reasons that more than 30% of cases failed to obtain positive results from culture vary and include low microbial counts, spontaneously sterilizing during the ocular inflammatory response of certain strains (eg, *Staphylococcus epidermidis*), or even noninfectious inflammations.[7,10,15,50,52]

In addition, the etiology of endophthalmitis might differ depending on the location in the world where the disease occurs. Whereas the microbiologic spectrum in Europe or in the US seems to be generally comparable,[7,46] it might be very different in other parts of the world. According to the EVS, 94.2% of culture-positive endophthalmitis cases involved Gram-positive bacteria; 70% of isolates were Gram-positive, coagulase-negative staphylococci, 9.9% were *Staphylococcus aureus*, 9.0% were *Streptococcus* species, 2.2% were *Enterococcus* species, and 3% were other Gram-positive species. Gram-negative species were involved in 5.9% of cases.[7] In contrast, a recent survey from India reported that Gram-positive bacteria accounted for only 53% of postoperative endophthalmitis cases, but 26% were Gram-negative isolates and 17% were of fungal origin.[53]

The advent of new therapeutic strategies for treating age-related macular degeneration, diabetic macular edema, and uveitis has led to a dramatic increase in intravitreal drug application. The risk of endophthalmitis after intravitreal injection is of rising concern.[23] Recent data, albeit limited, indicate that coagulase-negative staphylococci, as in postoperative endophthalmitis, appear to be the predominant pathogens in the development of endophthalmitis after intravitreal injection.[23] Less common organisms, including *Streptobacillus parasanguis*, *Mycobacterium chelonae*, and *Streptobacillus* species, as well as cases of noninfectious (sterile) endophthalmitis, especially in the context of intravitreal triamcinolone acetonide injections, have been reported in the literature.[22,23,54]

The majority of patients with postoperative endophthalmitis present with an acute onset and within seven days after surgery.[7,55] Chronic postoperative endophthalmitis is characterized by insidious inflammation and appears less common than the acute variety. Such cases can occur in the early postoperative period but usually manifest several weeks or month after surgery and often include less virulent bacteria and fungal pathogens.

Depending on the infecting organism, a correlation is thought to exist between clinical presentation and microbiologic spectrum. Gram-positive, coagulase-negative micrococci seem to cause less severe infections compared with more virulent Gram-negative and "other" Gram-positive organisms.[7] Streptococcal endophthalmitis often results in earlier onset and notably worse outcomes than infections by staphylococcal species. Endophthalmitis cases that failed to obtain positive results from culture tended to have a later onset and a better visual outcome.[55–59]

More severe infections are correlated with loss of red fundus reflex, afferent papillary defect, and light perception only at the time of initial presentation.[7] The presence of corneal infiltrates or cataract wound abnormalities are more strongly associated with more virulent Gram-negative and "other" Gram-positive organisms.[7] In addition, when more virulent pathogens are involved, signs and symptoms of endophthalmitis might be apparent earlier.[7] This is important because these cases seem to be significantly correlated with a worse visual outcome.

Specific factors influencing bacterial adhesion, including IOL material and surface irregularities, might have a role in the development of certain forms of endophthalmitis. *S epidermidis* carrying the intercellular adhesion locus might play a part in the pathogenesis of some forms of endophthalmitis.[60,61]

In most cases the diagnosis of endophthalmitis is made on clinical grounds. Any eye with inflammation that is out of proportion to the previous surgical trauma or greater than the predicted postoperative clinical course must be suspected as indicating postoperative endophthalmitis. If doubt cannot be erased, frequent observations should be conducted until the clinical course can be determined. Symptoms can be variable, from very little inflammation in the anterior chamber and the anterior portion of the vitreous to extremely painful panophthalmitis with no fundus view, corneal edema, or complete anterior chamber hypopyon[7,24,50] (see Figure 2).

According to the EVS, hypopyon can be seen in nearly 75% of patients, whereas ocular pain, often regarded as pathognomonic for endophthalmitis, was absent in 25% of patients.[7] In the European Society of Cataract and Refractive Surgeons Endophthalmitis Study (ESCRS) of prophylaxis for postoperative endophthalmitis after cataract surgery, hypopyon was present in 80% of culture-proven cases and 56% of unproven cases, resulting in an overall incidence of 72%.[55] Most common presentations include decreased vision, ocular pain and redness, corneal edema, and vitritis. In addition, retinal vasculitis, retinal hemorrhages, and posterior pole hypopyon may occur[7,24,50] (see Figure 3).

Posttraumatic endophthalmitis

Endophthalmitis is an important complication of open globe injury. About 25% of endophthalmitis cases are a result of ocular trauma and these are more often associated with a poorer visual outcome than otherwise similar globe injuries.[8] After posttraumatic endophthalmitis, only 22% to 42% of patients obtain a final visual acuity of 20/400 or better.[62–64]

The risk for developing endophthalmitis after sustaining open globe injuries is estimated at about 7%.[1,8,65] Increasing risk factors for endophthalmitis after ocular injury are dirty wound, lens capsule rupture, older age, initial presentation with a delay of more than 24 hours, and the presence of intraocular foreign bodies.[8,66–69] The incidence of endophthalmitis in cases of penetrating ocular trauma has been reported to range from 3.3% to 30% and after intraocular foreign body from 1.3% to 61%.[8,63]

A recent study from China, including 4968 eyes with open globe injury, found an incidence of posttraumatic endophthalmitis of 11.9%,[70] which is consistent with previous published data within the range of 2.6% to 54.2%.[70–73] In contrast, no evident correlation is found between the results of intraocular content culturing and development of posttraumatic endophthalmitis. Ariyasu and colleagues found that 33% of open globe injuries were culture-positive when aqueous was sampled, but none of these patients developed endophthalmitis.[66] In contrast, the prevalence of culture-negative cases of posttraumatic endophthalmitis has

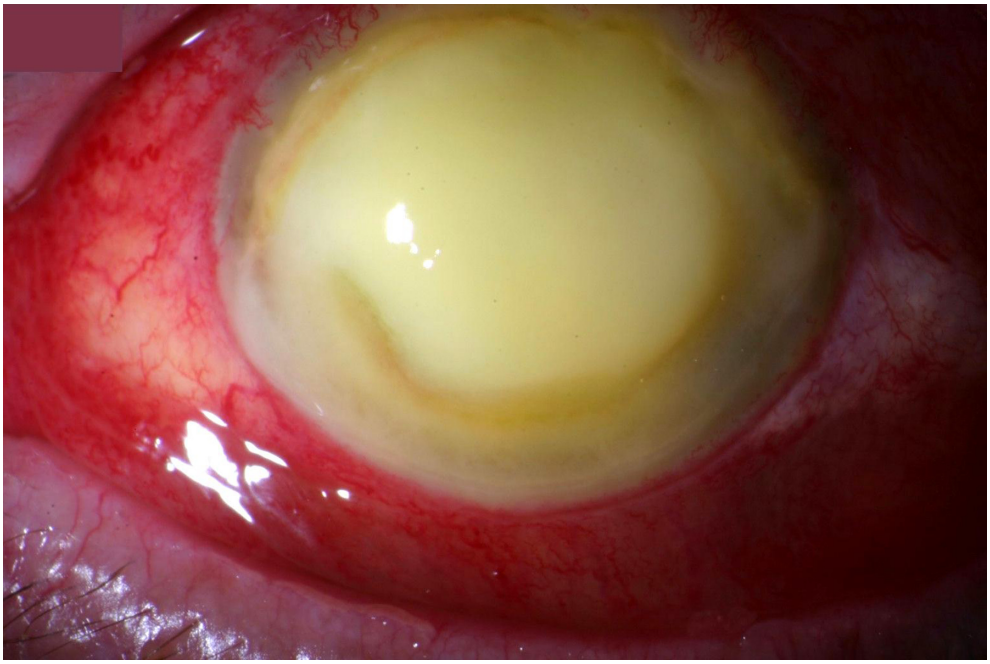

Figure 2 Leukocornea as a result of massive corneal edema and complete hypopyon in advanced *Staphylococcus aureus* endophthalmitis.

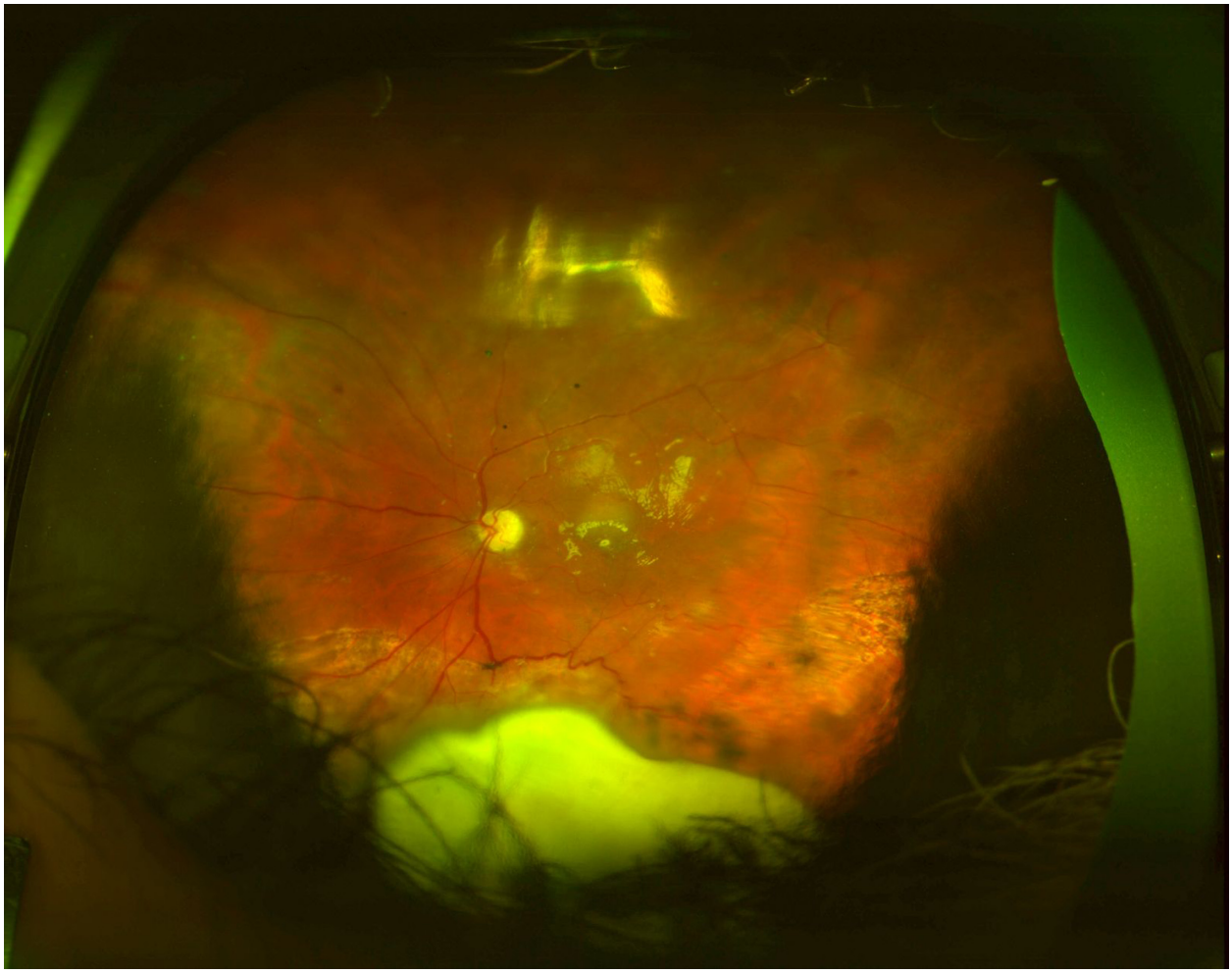

Figure 3 Posterior hypopyon in bacterial endophthalmitis imaged with Optomap widefield fundus imaging.

been reported to range from 17% to 42%.[67,68,74–76] Therefore, some authors do not suggest routine culture in all cases of open globe injury.[67]

Bacillus and *Streptococcus* are common species found in penetrating trauma with an intraocular foreign body.[68] This is important because *Bacillus* species are associated with more aggressive infection and are especially common in intraocular foreign bodies with organic composition.[64] Other species isolated include *S. epidermidis*, *Propionibacterium acnes*, *Pseudomonas* and *Streptococcus* species, Gram-negative organisms, fungi, and mixed pathogens.[8,64,70]

Initial evaluation of posttraumatic endophthalmitis must exclude occult or retained foreign bodies. If the fundus view is inadequate, computed tomography or, in eyes with self-sealing or previously sutured wounds, ultrasound may be helpful. Magnetic resonance imaging must be avoided because a retained foreign body might be magnetic.

Posttraumatic endophthalmitis may also be a result of contagious spread from an infected corneal, scleral, or adjacent wound.[8,68–70] Depending on the virulence of the infecting organism, posttraumatic endophthalmitis may occur within hours after the trauma or up to several weeks after injury.[8,68–70] Signs and symptoms must be evaluated with regard to the degree of traumatic injury and include decreased vision, pain greater than expected, lid swelling, corneal ring ulcer, anterior chamber inflammation, hypopyon, vitritis, or frank purulence.

Endogenous endophthalmitis

Unlike the origin in exogenous endophthalmitis, where the pathogen enters from outside the body into the eye, in endogenous endophthalmitis the infection is secondary to hematogenous spread from a distant infective source within the body. The endogenous form of endophthalmitis accounts

for approximately 5% to 10% of endophthalmitis cases.[3,4,77–80] It occurs when microorganisms in the bloodstream get into the eye, cross the blood–retina barrier, and infect the ocular tissue. Because of the higher blood flow, choroids and ciliary body are the primary focuses of infection in the eye with secondary involvement of the retina and vitreous.[3,5,79,81]

Risk factors for the development of endogenous endophthalmitis are mainly related to immunosuppression or to procedures that increase the risk for blood-borne infections. Most common factors include immunosuppressive diseases, such as diabetes mellitus, HIV infection, cancer, renal failure requiring dialysis, cardiac disease, long-term use of broad-spectrum antibiotics, steroids and other immunosuppressive drugs, major surgery, especially intra-abdominal surgery, intravenous hyperalimentation, indwelling intravenous catheters, and intravenous drug abuse.[3,4,77–80] Liver abscesses have been reported as the most common infectious origin,[3,82–84] followed by pneumonia, endocarditis, soft tissue infection, urinary tract infections, meningitis, septic arthritis, and orbital cellulitis.[3]

Causative organisms of endogenous endophthalmitis may be bacteria, as well as fungi, and rarely parasites. In contrast to exogenous forms of this disease, in endogenous endophthalmitis fungal pathogens play an important role.[3,4,85] However, the infecting organisms vary with geographic location.

In Europe and the US, *Streptococcus* species, *S. aureus*, and other Gram-positive bacteria account for two-thirds of bacterial endogenous endophthalmitis cases and Gram-negative isolates are found in only 32% of cases.[4,79] These numbers differ significantly from East Asia, where most cases of endogenous endophthalmitis are caused by Gram-negative organisms. In these areas, *Klebsiella* isolates count for 80% to 90% of positive cultures.[3,83] This difference might be attributable to the higher incidence of cholangiohepatitis and liver abscess in East Asian people than in the Western population.[3,82–84] However, during the last two decades, the number of endogenous ocular infections due to Gram-negative pathogens has dramatically increased in the Western world.[79] In contrast with its prominent role in acute postoperative endophthalmitis, *S. epidermidis* is only rarely found to cause endogenous endophthalmitis.[3]

Fungal endophthalmitis has become an increasing issue in western countries. *Candida albicans* followed by *Aspergillus* are the predominant species.[3,85] *Candida* species are a part of the human flora where they exist as commensals on the mucosal surface of the respiratory, gastrointestinal, and female genital tracts.[86] Where the immune system is compromised these organisms potentially become pathogenic. *Candida* species are the most common cause of nosocomial fungal infections.[87–89]

Candida chorioretinitis and endophthalmitis occur predominantly as a result of candidemia seeding the eye; cases in otherwise healthy individuals have rarely been reported.[90,91] Prospective studies demonstrated that patients with candidemia have a risk of developing endogenous fungal endophthalmitis of up to 49%.[2,81,92,93] However, a recently published study demonstrated that in patients with disseminated fungal disease, *Candida* chorioretinitis and endophthalmitis occurred in approximately 2.5% of cases.[94] These data might indicate that the current trend for prophylaxis and early treatment, as well as new drugs and treatment strategies for *Candida* infections, have decreased the incidence of fungal ocular complications dramatically.[94,95] Other isolates commonly found in endogenous fungal endophthalmitis are *Cryptococcus* and *Fusarium* species.[85,90]

Clinical findings in endogenous endophthalmitis may be similar to those in infections of exogenous origin. They include decreased vision, ocular pain, conjunctiva injection, hypopyon, corneal edema, vitritis, and reduced fundus view secondary to inflammation. Especially in cases of fungal infection, a subacute onset of floaters and blurred vision may be associated with ocular discomfort and photophobia.[94] In *Candida* infections, localized fluffy creamy white retinal or subretinal nodules may be associated with vitreous haze.[86,94] (see Figure 4). Early or peripheral fungal lesions may be asymptomatic, with patient referral for ocular consultation based on a positive blood culture or diagnosis of a systemic fungal infection. When more virulent pathogens are involved, widespread areas of perivascular infiltrates and hemorrhages with necrosis and retinal infarction can be seen.[5,8,96,97] In panophthalmitis, the whole globe and the orbital tissue may be involved.[5,84]

Management and perspectives

The prognosis of endophthalmitis, whether of exogenous or endogenous origin, is often poor. In general, endophthalmitis is recognized as an ominous disease, which runs a potentially devastating course, leaving only very limited visual function in many patients. Therefore, early diagnosis and treatment with antimicrobial therapy are fundamental to optimize visual outcome. In addition, the anticipated rise in ocular surgeries, as well as growing evidence that the rates of postoperative endophthalmitis might increase, underscore the importance of identifying effective methods of prophylaxis for improving surgical safety.

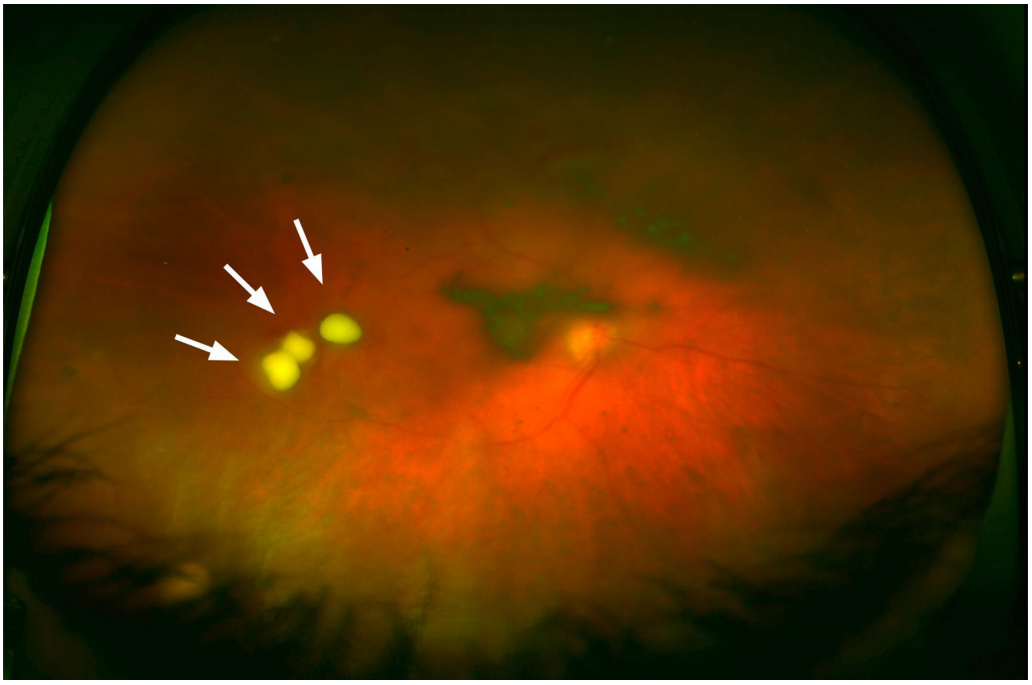

Figure 4 Localized epiretinal infiltrates of fluffy creamy white appearance in *Candida* endophthalmitis.

If endophthalmitis occurs, in most cases the diagnosis is based on clinical findings. Therapy is usually initiated empirically while microbiologic testing is being performed.

Early intervention is required and justified. With the introduction of intraocular sampling and intravitreal injection of antimicrobial agents, as well as the possibility for vitrectomy, management of endophthalmitis has entered a new era. The availability of such an armamentarium allows better management of endophthalmitis. However, knowledge about the likely organism that causes endophthalmitis, as well as the antimicrobial drug apt to be most effective, remains paramount.

Exogenous endophthalmitis

Historically, treatment of exogenous endophthalmitis was consisted mainly of intravenous antibiotics.[1] Nevertheless, most systemically administered antibiotics do not reach sufficiently high intraocular concentrations for effective treatment of severe intraocular infections such as endophthalmitis. A more effective way to achieve a high concentration of an antimicrobial substance within the eye and the infected tissue is intravitreal drug application. Therefore, the intravitreal injection of antibiotics has become the primary method of administration in the treatment of exogenous endophthalmitis.[1,98,99]

Unless there is no other unequivocal result from culturing, endophthalmitis therapy should cover Gram-positive organisms, which play a predominant role in exogenous endophthalmitis. Gram-negative coverage is also important because these organisms are associated with higher virulence and poorer outcome.

Current antibiotic standard protocols for intravitreal application are empirically based and include the peptide antibiotic vancomycin (1.0 mg/0.1 mL) for Gram-positive coverage,[7] in combination with the β-lactam antibiotic ceftazidime (2.25 mg/0.1 mL) for Gram-negative coverage.[7] In patients sensitive to β-lactam drugs, amikacin (400 μg/0.1 mL), an aminoglycoside antibiotic, might be considered instead of ceftazidime. However, a degree of retinal toxicity of amikacin has been reported.[100,101]

Gram-positive organisms reportedly have a 99% susceptibility to vancomycin.[102] Consequently, it has become a valuable component of endophthalmitis treatment. However, recently cases of vancomycin-resistant strains in endophthalmitis have been reported,[103,104] and emerging resistance of Gram-positive pathogens to vancomycin is a concern.[105,106] In addition, the EVS showed that only 89.5% of Gram-negative isolates were sensitive to amikacin or ceftazidime;[7] in India, susceptibility of Gram-negative bacteria to amikacin or ceftazidime has been reported as being only 68% and 63%, respectively.[107]

Use of fluoroquinolone antibiotics has been widely discussed as a potential alternative to current antibiotic treatment

protocols. In particular, the recently developed third- and fourth-generation fluoroquinolones, such as levofloxacin and moxifloxacin, with their enhanced activity against Gram-positive pathogens, offer broad-spectrum activity that covers most organisms commonly encountered in bacterial endophthalmitis.[108]

Moxifloxacin, and fluoroquinolones in general, penetrate well into the eye. After topical administration at two-hourly intervals, moxifloxacin reaches mean aqueous concentrations of 2.3 μg/mL.[109] A recent study demonstrated that anterior chamber levels achieved using moxifloxacin are higher than those obtained with any other topically administered fluoroquinolone antibiotic.[109] Nevertheless, intravitreal concentrations are 10 times lower than those in the anterior chamber. These levels are too low for effective treatment of intraocular infections.[110] Systemic moxifloxacin does not exceed anterior chamber concentrations. It reaches intravitreal concentrations 10 times higher than levels achieved by topical use, but to reach *S. aureus* and certain fluoroquinolone-resistant strains, higher concentrations are needed.[111] Therefore, direct intraocular application of such antibiotics seems useful.

Moxifloxacin is available as an unpreserved ophthalmic solution and covers both Gram-negative and -positive pathogens, including those most often implicated in the development of exogenous endophthalmitis.[112] An additional potential advantage of moxifloxacin for intraocular use might be the administration of only a single substance into the eye.

Several studies have investigated the potential use of fourth-generation fluoroquinolones, and especially moxifloxacin, as prophylaxis for and treatment of endophthalmitis.[113–119] In addition, pharmacokinetic data suggest intravitreal moxifloxacin is a useful alternative to current treatment protocols.[120] Its safety has been demonstrated both *in vivo* and *in vitro*.[113–117] An argument against use of moxifloxacin for the treatment of endophthalmitis may be that antibiotics from this group are widely used as topical antibiotics for treating superficial ocular infections and for preoperative prophylaxis. Moreover, concern exists about the emerging resistance of *S. aureus* and other Gram-positive isolates to third- and fourth-generation fluoroquinolones because of prophylactic use before and after intraocular surgery.[53,121–123]

These reports must be considered seriously, but it is noteworthy that sensitivity testing was determined *in vitro* and minimal inhibitory concentrations were based on serum levels (8 mg/mL). Recent data from toxicologic testing on ocular tissue indicate that moxifloxacin in doses up to 150 μg/mL did not result in significant toxicity on several ocular cell types.[113,114,116,117,124] Therefore, *in vivo* resistance appears to be very unlikely.

However, until these issues are resolved and its therapeutic role in endophthalmitis treatment is further elucidated, moxifloxacin should only be used in combination with an agent that is more reliable against Gram-positive pathogens.

A potential use of moxifloxacin for intracameral endophthalmitis prophylaxis in cataract surgery seems to be more reasonable. The ESCRS demonstrated that the prophylactic use of intracameral antibiotics helps to reduce the incidence of postoperative endophthalmitis after cataract surgery by 75%.[55] Therefore, prophylactic intracameral application of the β-lactam cefuroxime, together with the peptide antibiotic vancomycin, has become a beneficial and widely accepted practice for intracameral endophthalmitis prophylaxis in cataract surgery.[125]

However, in addition to the potential benefits, clinicians must consider that antibiotics from both groups are the mainstay of intravitreal treatment of endophthalmitis.[7] Consequently, one might argue that they should be reserved for this indication and not used for prophylaxis.

Due to its broad-spectrum properties, moxifloxacin is one of the most promising candidates in endophthalmitis prophylaxis as an intracameral adjunct during cataract surgery. Nevertheless, further investigations will have to clarify the role of moxifloxacin in this context.

Systemic fluoroquinolones and antibiotics in general have been discussed as adjunctive systemic treatments for postoperative endophthalmitis. In 1995, the EVS evaluated the role of systemic antibiotics and pars plana vitrectomy in the treatment of postoperative endophthalmitis.[7] The results of this study demonstrated that intravitreal antibiotics need not be supplemented with intravenous antibiotics in either acute or subacute postoperative endophthalmitis.[7]

Subconjunctival antibiotics may temporarily provide therapeutic levels to the anterior segment but, in general, they do not penetrate sufficiently into the vitreous cavity.[126] Further, large retrospective studies did not reveal an additional benefit compared with intravitreal antibiotic application.[127,128]

Corticosteroids are commonly used as adjunctive treatment in bacterial as well in fungal endophthalmitis. These agents are given to modulate the inflammatory response to infection that might help to reduce secondary damage. Topical and subconjunctival steroids are widely accepted. However, use of steroids given via the systemic and intravitreal routes in the treatment of endophthalmitis remains

controversial. A prospective, randomized trial demonstrated significantly less inflammation in endophthalmitis cases after intervention when 400 μg dexamethasone was applied intravitreally.[129] In contrast, visual outcome after 12 weeks was not affected.[129] A recent study found a trend toward better visual acuity with adjunctive dexamethasone in a smaller series of patients with endophthalmitis.[130] Other studies did not find any significant effect on inflammation or visual acuity.[131] Conversely, a retrospective, nonrandomized trial of 57 patients with postoperative endophthalmitis found a significantly worse visual outcome when intravitreal dexamethasone was added to therapy.[132]

Pars plana vitrectomy offers several potential benefits for endophthalmitis treatment. Results from the EVS showed that immediate vitrectomy provides a clear benefit in a well-defined subgroup; patients with light perception only at the time of presentation had a significant, threefold improved chance of obtaining a visual acuity of 20/40 after vitrectomy.[7] For diabetic patients with hand movement or better vision, at least a trend toward better final visual acuity after vitrectomy could be documented compared with vitreous tap and biopsy.[7] One reason for this may be that vitrectomy results in a reduction of pathogens, toxins, inflammatory materials, and opacities. Furthermore, vitrectomy enables samples to be obtained for culture.

A potential disadvantage of vitrectomy in endophthalmitis treatment might be that this technique is not ubiquitous and therefore effective treatment might be delayed. In addition, visualization of intraocular structures might be difficult, and vitrectomy might become desperate in highly inflamed eyes. Data from different studies are inconclusive, and the overall benefit of vitrectomy in endophthalmitis is still under discussion.[7,133,134] However, the EVS addressed the relative effectiveness of immediate pars plana vitrectomy.[7]

One prognostic factor for the final visual outcome seems to be the type of infecting organism isolated and, in one study, if no or equivocal growth was detected in culture, 80% of cases obtained a final visual acuity of 20/100 or better.[56] Infections with coagulase-negative staphylococci have also been associated with a final visual acuity of 20/100 or better in the EVS population (84%).[56] Due to their ability to induce significant inflammation, *S. aureus*, streptococci, and Gram-negative isolates seem to result in a worse visual outcome. Other strong predictors for poor visual outcome are initial visual acuity of light perception only, older age, corneal ring ulcers, compromised posterior capsule, abnormal intraocular pressure, afferent papillary defect, rubeosis iridis, and absence of the red fundus reflex.[56]

Endogenous endophthalmitis

In contrast with exogenous endophthalmitis, endogenous endophthalmitis requires systemic antimicrobial therapy. The primary source of infection in endogenous endophthalmitis is outside the eye, but within the body. Therefore, systemic cultures should be obtained.

Identification of the causative pathogen by blood, urine, or cerebrospinal fluid culture is successful in more than 75% of endogenous endophthalmitis cases.[3,4,135] Positive cultures from vitreous samples can be achieved much less frequently in endogenous endophthalmitis than in exogenous endophthalmitis.[3,4,135] However, especially in fungal endophthalmitis, the value of obtaining an ocular culture should not be underestimated because it may be the sole source of microbial growth. In addition to cultures, in certain cases and for fastidious organisms, fungal/bacterial DNA in intraocular fluid can be detected by polymerase chain reaction assay.[136–138]

The role of vitrectomy in endogenous endophthalmitis is not exactly defined. One reason for this could be that data from the EVS may not be applicable because the spectrum of causative organisms differs significantly in endogenous endophthalmitis. Although systemic and intravitreal antibiotics may be sufficient in milder forms of infection, vitrectomy seems to be helpful in severe cases of endogenous endophthalmitis because more virulent organisms, such as endotoxin-producing *Streptococcus* and *Bacillus* species, are commonly involved.[3,4] In addition, material from vitrectomy may provide a better source for culturing.

Patients with endogenous endophthalmitis need to have the type and extent of their disease diagnosed, complications detected, and underlying systemic cause or risk factors defined. A major target of antimicrobial therapy in endogenous endophthalmitis treatment is the source of infection, which is often guided by culture and susceptibility of the infecting organism.

Systemic antimicrobial therapy is the mainstay of endogenous endophthalmitis treatment. In most cases, treatment is initiated empirically and the infecting organism presumed to be that causing systemic infection. For intravitreal antibiotic application in bacterial infections, as with exogenous endophthalmitis treatment, vancomycin (1.0 mg/0.1 mL) for Gram-positive coverage or in combination with the β-lactam antibiotic ceftazidime (2.25 mg/0.1 mL) or amikacin (400 μg/0.1 mL) is recommended for Gram-negative coverage. In general, systemic therapy must be continued for several weeks to ensure eradication of the infection.

Fungal endophthalmitis

Only a small number of exogenous endophthalmitis cases are thought to be fungal. However, in some tropical countries, up to 50% of central corneal ulcers are caused by fungi,[139–142] and a recent review of more than 40 cases of exogenous fungal endophthalmitis revealed that almost 50% of these cases were associated with fungal keratitis.[99] (see Figure 5). Therefore, exogenous fungal infections of the eye are of increasing concern.

If exogenous fungal endophthalmitis occurs, it is mostly caused by molds (mainly *Fusarium* and *Aspergillus* species).[99] Nevertheless, most cases of fungal endophthalmitis are a result of endogenous fungal spread into the eye. The most commonly reported causes of endogenous fungal endophthalmitis are *Candida* species (>50%) followed by *Aspergillus* and *Fusarium* species.[8,90,143–145]

In endogenous fungal endophthalmitis, treatment should be instituted as soon as the diagnosis is made, under close supervision by the attending physician. Treatment guidelines for mild forms of fungal chorioretinitis and vitreitis suggest systemic antifungal therapy combined with serial ophthalmologic examinations.[146,147] Surgical intervention combined with systemic and intraocular antifungal drug application is warranted in cases of moderate or severe vitreous involvement.[146,147]

Most current treatment protocols recommend amphotericin B (5–10 µg/0.1 mL) and triazoles as primary therapeutic options. Both can be given systemically and intravitreally. However, the intraocular penetration of amphotericin B after topical or systemic treatment is limited, and intraocular use is associated with retinal toxicity.[148] In addition, many fungal pathogens affecting the human eye are not susceptible to these agents.[90,143] Recently developed second-generation triazole derivates (eg, voriconazole) seem to be promising alternatives. Voriconazole can be given either systemically or intravitreally. It penetrates well into the ocular tissue after systemic administration.[149] Severe systemic side effects seem to be less common than with amphotericin B and several *in vitro* studies indicate that the safety profile of voriconazole after intravitreal application may be superior to that of amphotericin B.[150–154] The general *in vitro* susceptibility of *Candida, Aspergillus*, and *Fusarium* species to voriconazole are almost 100%.[90] Numerous case reports indicate that voriconazole treatment has been successful where amphotericin B or fluconazole has failed, even in cases of drug-resistant fungal keratitis and endophthalmitis.[152,155–160]

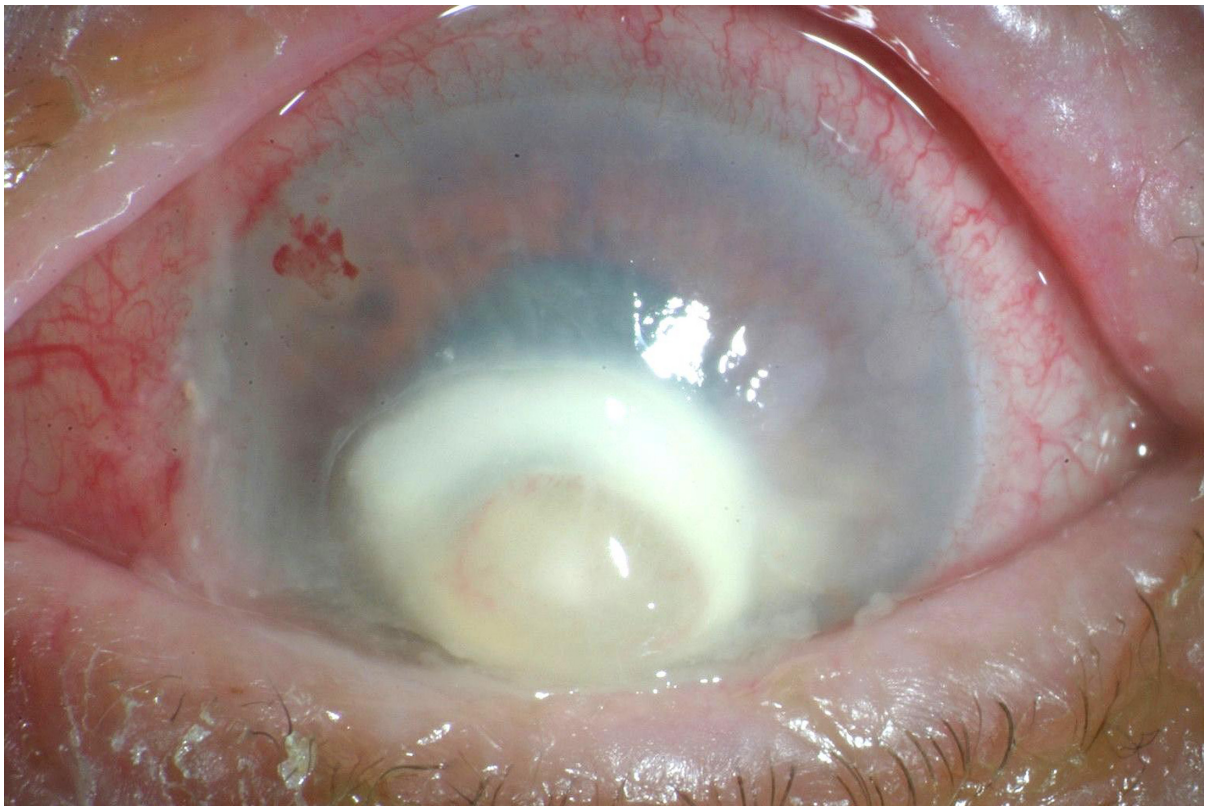

Figure 5 Exogenous fungal endophthalmitis with corneal ulcer.

In a situation where adequate and timely treatment is essential, eyes with endogenous fungal endophthalmitis may achieve a far better final visual acuity than eyes with bacterial infections.[6,161] In a larger series of endogenous fungal endophthalmitis cases, 65% of eyes achieved 20/400 or better acuity.[2] Nevertheless, in endogenous fungal endophthalmitis the organism isolated is critical for prognosis. *Candida* endophthalmitis seems to result in better outcomes than endoophthalmitis caused by *Aspergillus* or other fungi.[2,5]

Another potential treatment for endogenous fungal endophthalmitis is caspofungin, the first member of a recently introduced new class of antifungal agents known as the echinocandins.[162,163] Because of their different mechanism of action, these agents are an important therapeutic alternative to currently available antifungal treatments for invasive fungal infections. Caspofungin has potent antifungal activity against *Candida* and *Aspergillus* species, which are the predominant fungal pathogens in fungal endophthalmitis. Recent reports suggest that systemic caspofungin combined with voriconazole might be an effective treatment of endophthalmitis caused by *Candida, Acremonium*, and *Aspergillus* species.[159,164–166] However, the intraocular penetration properties of caspofungin after intravenous application remain unclear.[167,168] One patient with advanced endogenous endophthalmitis failed to respond to caspofungin, and after nine days of a standard systemic dosage, no caspofungin could be detected intravitreally.[167]

Clinical experience with caspofungin in endophthalmitis treatment is limited. To date, no data are available on the potential intraocular use of caspofungin. First results from *in vitro* testing seem to be promising[169] but need further clarification *in vivo*. Nevertheless, due to their unique mechanism of action and their high activity against yeasts and mold, including those commonly affecting the eye,[170–172] caspofungin and other emerging drugs of this group might become more prominent in future treatment strategies for fungal endophthalmitis.

Conclusion

Endophthalmitis is one of the most devastating complications after ocular surgery or trauma and in people with systemic infection. Treatment of endophthalmitis remains challenging. Early diagnosis and treatment are essential to optimize visual outcome. Intravitreal antimicrobial drug application achieves the high intraocular substance levels needed for effective endophthalmitis treatment.

Vitrectomy seems to provide several substantial benefits in the treatment of endophthalmitis and remains accepted as a treatment option which is supplementary to intravitreal antimicrobial therapy in patients with moderate or severe disease. The EVS addressed the relative effectiveness of immediate pars plana vitrectomy after postoperative endophthalmitis.[7] However, a general advantage of vitrectomy in endophthalmitis is still under discussion.

In general, for exogenous endophthalmitis treatment, intravitreal antibiotics need not be supplemented with intravenous antibiotics. In contrast, most cases of endogenous endophthalmitis, where the primary focus of infection is outside the eye, require systemic antimicrobial therapy. Supplementary intravitreal drug application and vitrectomy may be supportive.

In fungal endophthalmitis, vitrectomy and intravitreal amphotericin B are indicated in case of severe vitreous involvement. Recent advances in therapy using antimycotic drugs, including the second-generation triazole agent voriconazole and the echinocandin caspofungin, may offer new treatment options to manage fungal endophthalmitis, but these drugs need further evaluation.

Disclosures

The authors do not have any commercial or financial interest in any of the materials or methods used in this study.

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