Chapter 9

Endophthalmitis: Experience from a Tertiary Eye Care Center

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Additional information is available at the end of the chapter

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1. Introduction

Endophthalmitis is a devastating ocular inflammatory process that can lead to blindness. In endophthalmitis, there is inflammation of the vitreous cavity along with the retinal and uveal components of the eye. [1] In the vast majority of cases of endophthalmitis, inflammation is triggered by an infectious agent. [1, 2] The source of such infectious agent could be an exogenous such as following trauma or after an eye surgery (Figures 1 & 2). Eye surgeries may be either intraocular (such as cataract, glaucoma, retina) or extra-ocular such as refractive or muscle surgery. Post-operative endophthalmitis could be either sterile or infectious. The infectious agent encountered following the eye surgery or trauma is usually the organisms harboring the outer surface of the eye. [2, 3] Bacterial infections are the most common cause of post-operative endophthalmitis, and Gram-positive isolates account for the majority of these cases. [2] Fungal infections may occur, particularly in association with the use of contaminated ocular irrigation fluids. [4, 5] Patients having previous history of glaucoma surgery with thin blebs and penetrating keratoplasty may also be vulnerable to risks of developing endophthalmitis. Endogenous endophthalmitis is less common and occur secondary to hematogenous dissemination and spread from a distant infective source in the body. [2, 3, 6, 7] In patients with endogenous endophthalmitis, some of the predisposing risk factors may include diabetes, cardiac disease, and malignancy. [2, 3] The common foci of infection may be urinary tract infection, septic arthritis, pneumonia, and endocarditis. Less common causes of endogenous endophthalmitis include orbital and periorbital cellulitis and in rare cases facial cellulitis. [8] Recently, endophthalmitis was a major reason for evisceration among the 187 cases reported from a tertiary eye care center. [9]

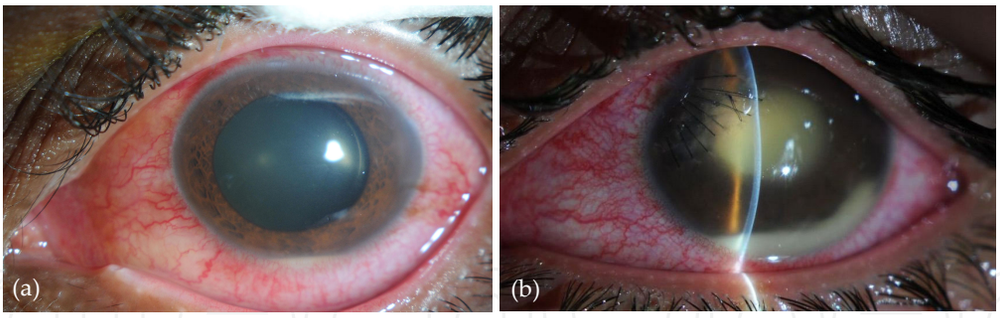

Figure 1. Signs of early post-operative endophthalmitis in patients after intraocular surgery (a) and after repair of traumatic eye injury (b) after injury.

2. The etiology of endophthalmitis

The spectrum of the microorganisms causing endophthalmitis may differ in different parts of the World. According to the Western literature, over 75% of culture positive cases of endophthalmitis are due to Gram-positive bacteria that includes, Staphylococcus species, Streptococcus species, Enterococcus species, and other Gram-positive species. [2, 3] Gram-negative species may account for up to 6% of endophthalmitis cases. Studies from other countries such as India reveal that Gram-positive bacteria may account for 53% of post-operative cases of endophthalmitis and up to 26% may be due to Gram-negative bacteria, while rest 17% may be due to fungal infection. [2, 3, 10, 11]

3. Presenting features of endophthalmitis and diagnosis

An eye with inflammation that is out of proportion to the predicted post-operative clinical course or previous trauma than expected should be suspected of having endophthalmitis. [1-3, 12] Majority of patients with post-operative endophthalmitis present with an acute onset usually within a week after surgery. [12] Most common presentations include decreased vision, ocular pain, photophobia, redness, corneal edema, hypoyon and vitritis (Figure 2). In addition, retinal vasculitis, retinal hemorrhages, and posterior pole hypoyon may also occur. Chronic post-operative endophthalmitis is characterized by insidious inflammation and appears less common than the acute type. Patients with chronic post-operative endophthalmitis usually present several weeks after surgery and often these patients have infection with less virulent bacterial and fungal pathogens. [13]

Progressive vitritis is one of the key findings in cases of infectious and non-infectious endophthalmitis, and in the vast majority of cases, a hypopyon can be seen at the time of initial presentation. [2, 3] Absence of a fundus red-reflex, presence of relative afferent pupillary defect (RAPD) and light perception vision at the time of initial presentation may be associated with worse final visual outcome (Figure 3). Infections with virulent organisms present with

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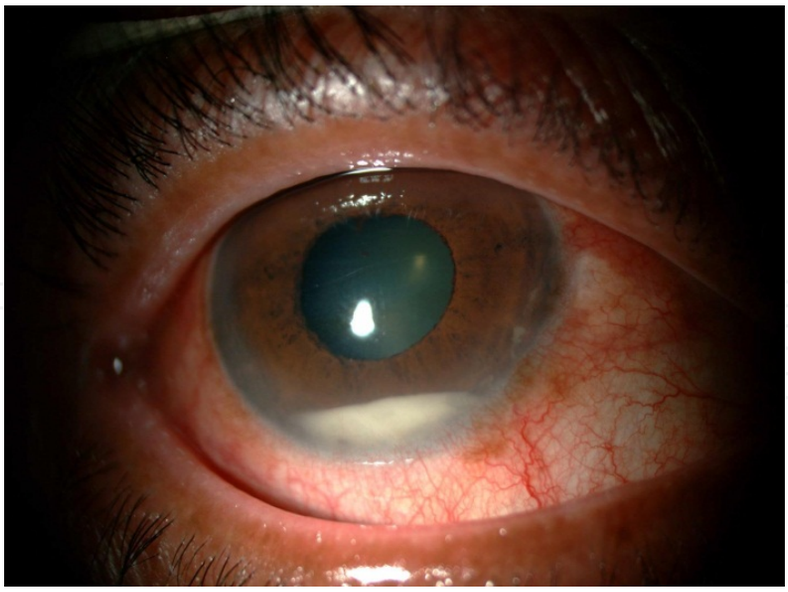

Figure 2. Anterior chamber reaction and hypopyon in a patient with endophthalmitis.

aggressive signs and symptoms of endophthalmitis. Other risk factors associated with worse visual outcome may include presence of corneal infiltrate, wound abnormalities after cataract surgery and virulent pathogens. According to the Endophthalmitis Vitrectomy Study (EVS), [10] a prospective, randomized clinical trial of post-operative acute endophthalmitis, hypopyon was documented in 75% of the enrolled patients and according to the European Society of Cataract and Refractive Surgeons Endophthalmitis Study (ESCRS), hypopyon was present in 72% of patients having endophthalmitis. [11, 14] Pain was absent in almost one-fourth of patients enrolled in the EVS at the time of their initial presentation. Untreated endophthalmitis may lead to panophthalmitis which may present with increased pain, proptosis, limitation of eye movements, eyelid edema, intense conjunctival chemosis, corneal edema, infiltrate, complete anterior chamber hypopyon and even eye perforation. [15]

Patients having full blown endophthalmitis within days after the surgery often have infection due to Staphylococcus or Streptococcus species or alpha-hemolytic Streptococci species of the 'viridans' group during which vision can be lost over 12 hours if no intervention is undertaken. [10, 16-18] A diagnosis of endophthalmitis should be entertained for any patient presenting within 6 weeks after surgery with pain and loss of vision. In most cases, the diagnosis of endophthalmitis is made on clinical grounds. Ultrasonography is necessary for the clinical evaluation of patients with suspected infectious endophthalmitis in the absence of a good fundus view. Rapid detection and identification of the causative pathogens is crucial for vision-saving treatment. [19] Conjunctival and corneal swabs are usually not helpful, as the correlation with the microorganisms isolated is very low. [2, 10, 11, 18] Similarly, microorganism identification from the anterior chamber is less successful as compared to vitreous tap in cases of suspected endophthalmitis. Depending on the visual acuity, an anterior chamber tap and a vitreous tap along with intra-vitreal antibiotics may be indicated to confirm the infection and treat the cause. Samples of aqueous and vitreous should be collected

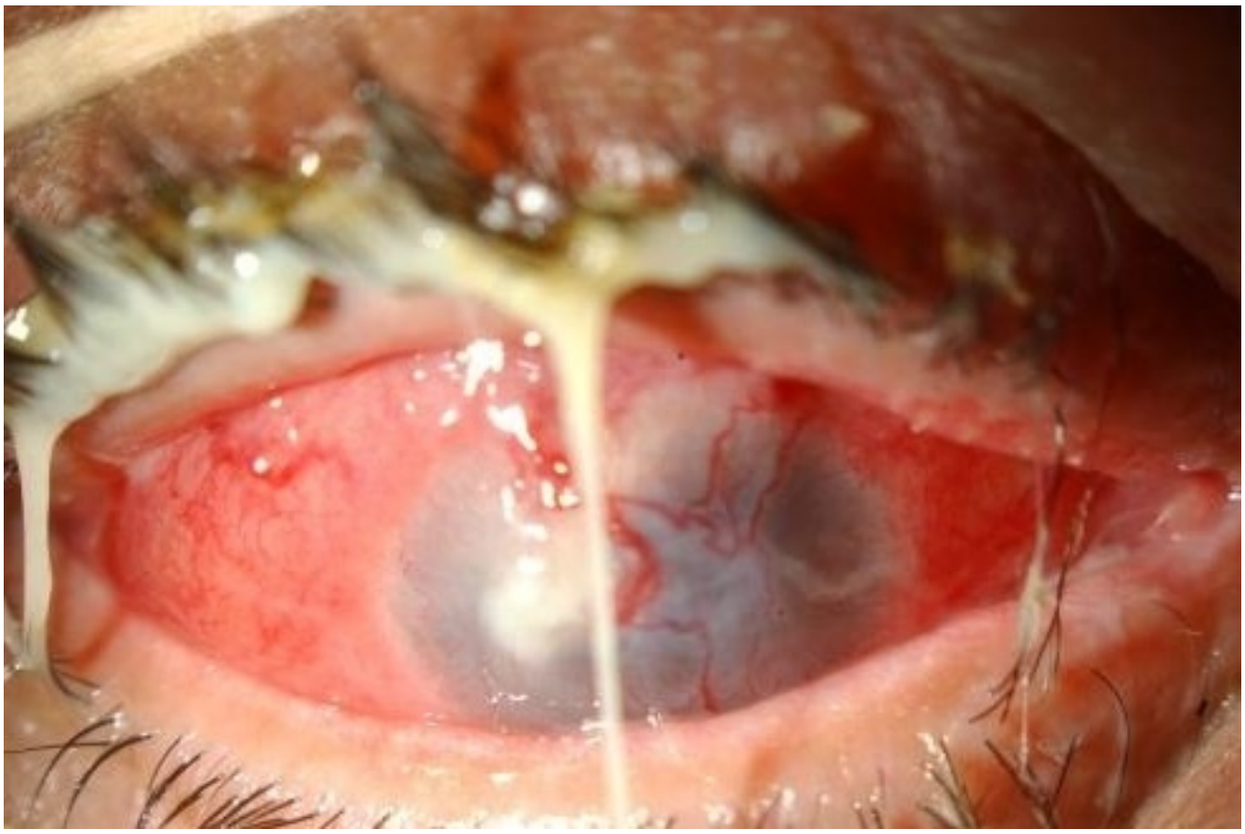

Figure 3. External photograph of a patient with history of cataract surgery who presented with severe conjunctivitis, corneal opacification and vascularization was found to have evidence of endophthalmitis.

from these patients for Gram staining, culture, and Polymerase Chain Reaction (PCR) assay. [20] Anterior chamber and vitreaous specimens obtained should be directly inoculated on to the culture media at the time of procedure. If any of these investigations yield a positive result, the case can be classified as a proven case of infective endophthalmitis; otherwise the case should be classified as presumed unproven endophthalmitis. Each unproven case should be carefully considered if there is evidence of the Toxic Anterior Segment Syndrome (TASS) or non-infective uveitis when the case is not considered infective otherwise. [21, 22]

Patients presenting late after surgery with uveitis that has not responded to a course of corticosteroids need to be investigated for chronic infectious endophthalmitis. One should always consider the possibility of having an infection within the capsular sac with Propionibacterium species, Corynebacterium species, or coagulase negative Staphylococci. [1, 3, 23, 24] Such infections may persist years after the ocular surgery and require an anterior chamber and vitreous tap. Some of the bacterial organisms may be sequestered within macrophages surrounded by lens capsule. In these circumstances, removal of the intraocular lens or exchange to prevent recurrent or persistent endophthalmitis may be necessary. These patients may present initially as having uveitis and hypopyon within 6-8 weeks of surgery, which fails to respond to corticosteroids and needs eventual vitrectomy with intra-vitreal antibiotics and often the removal of the intraocular lens (IOL). In chronic saccular endophthalmitis, there is granulomatous inflammation and characteristic white capsular plaque.

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[13, 23] A"trial of therapy"with Clarithromycin or Azithromycin may be considered since these drugs penetrate well into the tissue, and Propionibacterium acnes is very sensitive to these drugs. [13, 24, 25] For unknown reasons, culture-negative endophthalmitis may respond well when the patient is treated with clarithromycin. [25] One needs to be aware, that Propionibacterium acnes may appear as a Gram-variable coccobacillus when the specimen is obtained from the anterior chamber or vitreous. The PCR technique has been found to be more sensitive to identify bacteria in these situations. [20] Molecular techniques using multiplex or broad-range PCR may enable rapid detection and identification of causative pathogens in ocular infectious diseases. In certain circumstances, PCR technique may provide the results of the causative micro-organism within 6 hours of biopsy. The PCR method offers much improved pathogen detection especially in the case of chronic endophthalmitis with low pathogen counts. PCR was extensively evaluated in the multi-center European prophylaxis study of postoperative endophthalmitis following cataract surgery and was found to be useful in identifying 6 out of 20 pathogens causing endophthalmitis where standard Gram-stain and cultures results were found to be negative. [11] Multiplex PCR has the drawback of allowing only a limited number of genes to be analyzed in one reaction, and pre-identification of the species level is required. Analysis of amplicons by DNA sequencing after broad-range PCR, are the most used techniques for identifying DNA, but the time and effort associated with data analysis lead to some limitations. Therefore, improved high-throughput genotyping methods that are sensitive and discriminative may be desired. DNA microarray technology has been found to be a promising genotyping method that allows simultaneous identification of a wide variety of genes and rapid determination of the genetic profile of a microorganism in a single experiment. DNA microarray technique may be useful for genetic screening and identification of microorganisms in cases of suspected infectious endophthalmitis. [26]

4. Exogenous bacterial endophthalmitis

Patients may present days or several weeks following cataract or other ocular surgery with reduced visual acuity (VA) and signs of inflammation in the anterior chamber along with other evidence suggestive of endophthalmitis. [27, 28] Intraocular surgery remains the most common cause of endophthalmitis considering the number of cataract surgeries being performed around the World. [12] The infection may also occur following glaucoma surgery, retina surgery and even following strabismus surgery. [29, 30] Ocular trauma remains another major source of endophthalmitis especially in cases of Retained Intraocular Foreign Body (IOFB). Symptoms of acute endophthalmitis in these patients may include decreased vision, pain, swollen eye lids, conjunctival chemosis with discharge and photophobia. [31] There may be signs of conjunctival and corneal edema, anterior chamber inflammation with inflammatory cells, hypopyon or fibrin clot (Figure 4). Presence of vitreous haze may prevent clear view of the fundus. Loss of the red reflex may be a poor guide to the general state of the vitreous, which may be most opaque anteriorly where the inflammatory process has begun. In some instances, signs of endophthalmits following ocular surgery or trauma may appear soon. For example, acute suppurative endophthalmitis due to Streptococcus pyogenes may occur days

after cataract surgery in which case the patient may present with swollen eyelid, opaque cornea, conjunctival chemosis and significant pain. [2, 3] Endophthalmitis elicits an aggressive inflammatory reaction that can result in the breakdown of the blood-ocular barrier. Such acute inflammatory process may need to be controlled in order to preserve vision by protecting the uveal tissue. Intra-vitreal Dexamethasone at the time of vitreal biopsy and intra-vitreal antibiotics has been found to be very helpful in minimizing uveal tissue damage.

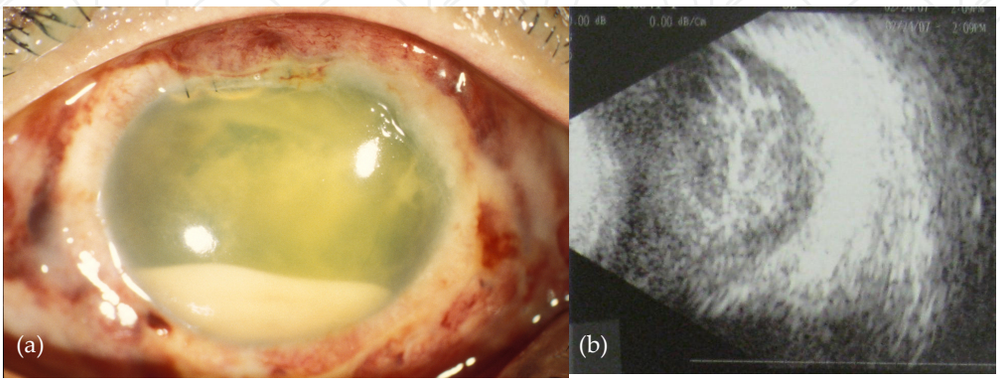

Figure 4. External photograph of a patient's right eye who presented with decreased vision, pain, tearing, redness and photophobia several days after having penetrating trauma to his right eye. He was found to have conjunctival chemosis along with anterior chamber hypopyon (a). Ultrasonography revealed evidence of vitreous opacification suggestive of endophthalmitis (b).

5. Risk factors for the development of the post-operative endophthalmitis

The relative risks of developing post-operative endophthalmitis depend on a number of factors, including the presence of eyelid or conjunctival diseases, the patient's general health, the use of immunosuppressant medications, the type of intraocular surgery, the type of intra-ocular lens (IOL) used and intra-operative complications. [31] Diabetes has been associated with endophthalmitis; one study revealed that among the 162 patients who were treated for endophthalmitis, 21% of them had evidence of diabetes. In that study, patients with diabetes had poor visual outcome and the possibility was related to these patient's having poor wound healing ability. This association was also observed in the EVS trial, patients with diabetes had a trend toward worse vision at baseline, higher incidence of positive cultures and need for additional surgeries during follow-up. [33] Specific eyelid or peri-orbital diseases such as blepharitis, ectropion, entropion and paralytic disorders may enhance the chance of post-operative endophthalmitis. It is recommended that minimizing the contact between IOL and the ocular surface may reduce the risk of endophthalmitis at the time of its implantation. Risk of developing endophthalmitis has been reported to be lower with the introduction of injectable IOLs as compared with foldable lenses since injectable lenses avoid the contact with ocular surface. There is also evidence that certain kinds of materials used for manufacturing intraocular lenses may have higher incidence of endophthalmitis. For example, PMMA lenses may be associated with a higher rate of endophthalmitis as compared with acrylic IOLs. [5,

34, 35] Intra-operative complications, specifically posterior capsular break or vitreous loss may also be a cause of increased risk of post-operative endophthalmitis.

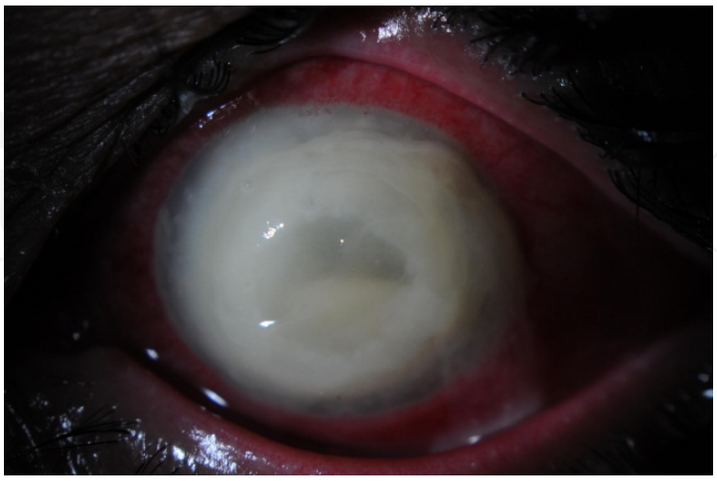

Figure 5. External photograph of a patient's left eye showing failed corneal graft due to infectious keratitis and endophthalmitis.

Procedures, such as penetrating keratoplasty, trabeculectomy, and glaucoma drainage device implantation have all been reported to cause endophthalmitis which are higher than simple cataract operation (Figure 5). [36] Endophthalmitis can occur in 0.2-9.6% of cases following glaucoma surgery depending on the procedure and the use of 5-fluorouracil or mitomycin-C as anti-fibrotic agents. [3, 29, 30] Rare causes of endophthalmitis have been reported following phakic IOL implantation for refractive errors and extra-ocular surgeries such as excision of pterygium, strabismus surgery and sclera buckling procedure. [4] Secondary IOL implantation has been found to be associated with the highest risk for developing endophthalmitis (0.2%–0.37%) and PPV with the lowest (0.03%–0.05%). Other sources of infection include, contaminated surgical equipment, irrigation fluids and poor patient hygiene. Other risk factors for the development of post-operative endophthalmitis include canaliculitis, acute and chronic dacryocystitis and anti-glaucoma aqueous drainage devices. [36-39] It is recommended that patient having any evidence of chronic canaliculitis, dacryocystitis should only undergo any intraocular surgery after resolution of their infection. Patients having chronic dacryocystitis may harbor multiple micro-organisms which may be resistant to the commonly prescribed post-cataract surgery prophylactic antibiotics. It has been reported that almost 10% of patients having chronic dacryocystitis in the setting of nasolacrimal duct obstruction may develop acute dacryocystitis requiring systemic antibiotics. [37-39]

6. Endophthalmitis following cataract surgery

Over 90% of post-operative endophthalmitis develop as a complication of cataract surgery since it is the most common intraocular surgery performed by ophthalmologists worldwide

(Figure 6). [3, 40] A century ago, the incidence of endophthalmitis after cataract operations was over 10% which has dramatically decreased since the advent of antibiotics and the utilization of aseptic techniques. During the era of extra capsular cataract extraction under improved hygiene conditions, the infection rate has fallen below 0.1% in the developed countries. [2] In the absence of prospective randomized case-controlled studies, the true incidence of endophthalmitis may be difficult to determine given its rare occurrence within a single center. [1-3] Recently, clinical features, microbiology and final visual outcome as well as the incidence of acute-onset post-operative endophthalmitis after cataract surgery have been reported from Saudi Arabia by Al-Mezaine et al, [12] from a single tertiary eye care center over a 10-year period. According to their retrospective series, the incidence of acute-onset endophthalmitis after cataract surgery was 0.068% and the most common presenting features were pain and poor red reflex. Staphylococcus species and Streptococcus species were the most common micro-organisms encountered. Visual outcomes were good in cases of endophthalmitis following phacoemulsification and in those caused by Staphylococcus epidermidis and worse in cases that were caused by Streptococcus species. Overall, clear corneal phacoemulsification had a 1.73-fold higher risk for acute endophthalmitis than extra-capsular cataract extraction but the visual outcome was worse in post-extra capsular cataract extraction cases. In this series, the poor visual outcome was associated with more virulent organisms and delayed presentation. [12]

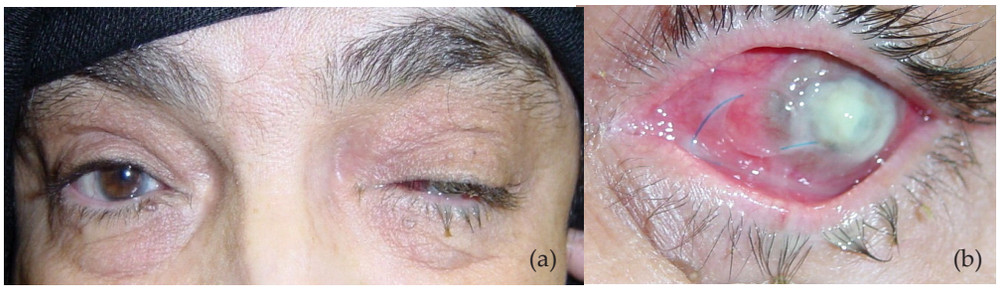

Figure 6. External photograph of a 65-years-old female who underwent uneventful cataract extraction along-with intraocular lens implantation in her left eye. Two weeks later, she presented with painful left eye and complete loss of vision (a). She was found to have necrosis of her left corneal wound and extrusion of the implanted intra-ocular lens (b).

A review of the literature has provided a greater number of patients with risk factors for the development of endophthlamitis. [2, 3, 40] In a systematic review of the literature by Taban et al, [41] of 215 studies of 3,140,650 cataract extractions published between 1963 and 2003, a higher overall post-cataract endophthalmitis rate occurred between 2000 and 2003 (0.265%) as compared with between 1963 and 2000 (0.128%). The rate of endophthalmitis was higher with clear cornea incision (0.189%) versus scleral incision (0.079%) between 1992 and 2003. In another large population-based review of United States Medicare beneficiary claims between 1994 and 2001 of 447,627 cataract operations, 1026 cases of presumed endophthalmitis were noted and an increased incidence was associated with the introduction of clear cornea incision. [42] The incidence of endophthalmitis was higher from 1998 to 2001 (2.5 per 1000) as compared with between 1994 and 1997 (1.8 per 1000), possibly reflecting the increasing

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use of clear corneal incisions during this time period. Some limitations to these larger studies are their being retrospective in nature that may differ in methodology and definitions. In addition, decreased preoperative use of povidine-iodine and fewer administrations of sub-conjunctival injections at the end of surgery may have occurred as ophthalmologists converted from retro-bulbar or peri-bulbar anesthesia to topical anesthesia during this time period which may be confounding factors leading to an increased rate of endophthalmitis. [2, 3, 42]

Following intraocular surgery, leak-proof closure of the corneal incision is recommended to limit access of microorganisms to the anterior chamber. [43] Evidence indicates that with the clear corneal incision, in the absence of sutures, the wound appears to be loose allowing microorganisms to enter into the eye and subsequent development of endophthalmitis. Type of wound closure may also be an important determinant of the endophthalmitis following PPV. [3, 44] As compared to the cataract surgery, the incidence of endophthalmitis following PPV is low and ranges between 0.03-0.05%. [3] However, even after PPV, the use of sutureless and minimal incision techniques have been found to be associated with higher incidence of post-operative endophthalmitis than standard closure technique.

7. Intra-operative antibiotic prophylaxis

Antibiotics are used in the irrigating solution as a prophylaxis by many ophthalmologists around the world during the routine cataract surgery operations. While it is suggested that the addition of antibiotics to the irrigating solution may have a protective effect, it has not been possible to reduce the incidence of endophthalmitis in any prospective clinical study. [45] Most of the studies on the incidence of endophthalmitis following intraocular surgery have been obtained either from the retrospective studies or from studies of antibiotic use where there was no control group. Prophylactic intra-cameral irrigation of antibiotics such as Cefuroxime and Vancomycin has been found to be beneficial against post-operative endophthalmitis. [46] The ESCRS demonstrated that the prophylactic use of intra-cameral antibiotics may help to reduce the incidence of post-operative endophthalmitis after cataract surgery by 75%. [47]

8. Post-operative antibiotic prophylaxis

Over the past several decades, sub-conjunctival antibiotics injection has been advocated as a prophylaxis against infection after most of the intraocular surgeries. [1-3] At the time of sub-conjunctival antibiotic injection, corticosteroids are frequently used as adjunctive treatment to reduce the inflammatory response due to infection that might help to reduce secondary damage. No study, however has proven that this method has any prophylactic effect on the prevention of endophthalmitis. [1] A retrospective report found one case of endophthalmitis after 8856 surgeries using sub-conjunctival antibiotics and 9 cases of endophthalmitis fol-

lowing 5030 surgeries without having sub-conjunctival injections. [48] Sub-conjunctival antibiotics may temporarily provide therapeutic levels in the anterior segment but do not penetrate sufficiently into the vitreous cavity, and hence larger retrospective studies did not reveal any additional benefit compared with intra-vitreal antibiotic application.

A careful wound construction with a minimum wound leakage and the placement of sutures when necessary is recommended to prevent incident of any post-operative infection. [19, 43] Optical coherence tomography may show variations in gaping of un-healed wounds and Indian ink may migrate through un-healed wound into the anterior chamber. Experience has shown that it may take upto a week before the epithelial surface heals completely to have the wound become water-tight. Therefore, it may be necessary that post-operatively one may consider addition of topical antibiotics drops. Some studies have suggested that silicone IOLs may have a three times higher risk of developing post-operative endophthalmitis than acrylic IOLs. On the other hand, hydrophilic heparin-coated IOLs have demonstrated their lower adherence for Staphylococcal organisms to the lens surface. [1-3] In order to reduce the risk of infection following clear corneal incisions, the use of topical antibiotic drops for 1-2 weeks after the surgery has been recommended. [49] Usually broad spectrum antibiotics are used to cover the most commonly encountered microorganism. These antibiotics are administered topically 4-6 times daily.

9. Toxic anterior segment syndrome (TASS)

One may need to differentiate between the postoperative endophthalmitis from the less common cases of TASS. The TASS presents acutely within the first 48-hours after surgery with pain and blurred vision. In these cases, there may be diffuse corneal edema of the whole cornea along with endothelial cell damage. One may see evidence of a small hypopyon along with signs of iritis that may result in iris atrophy. TASS is usually a toxic reaction in the absence of any infectious process and occurs in groups following intraocular surgery. [21] Acute endopthalmitis due to Bacillus cereus after cataract surgery have a fulminant onset with extremely high intraocular pressure, corneal edema and intense pain which may look like TASS. [22] However these eyes rapidly progress to develop corneal infiltrates, scleral and uveal tissue necrosis with hyphema, brownish exudates in anterior chamber and necrotizing retinitis within hours despite immediate intra-vitreal antibiotics and vitrectomy. One may see gram-positive bacilli from the aqueous. The organism is sensitive to conventional antibiotics except penicillin. Because acute onset endophthalmitis due to Bacillus cereus has an onset within 12 to 24 hours of intraocular surgery, it simulates TASS in the first few hours but then the clinical course of endophthalmitis due to Bacillus cereus is marked by rapidly worsening necrotizing infection, leading to very poor outcomes despite early institution of appropriate therapy. [22] One must closely observe every case of TASS that presents with intense pain and extremely high IOP and rule out acute post-operative endophthalmitis due to Bacillus cereus with microbiologic testing.

Different causes of TASS have been reported and timely action is required for proper diagnosis and treatment. Variety of stimuli including bacterial endotoxin (lipopolysaccharide

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cell wall of Gram-negative bacteria) from water within the ultrasound machine used for instruments cleaning or even from contaminated but sterile water used to make steam in an autoclave and viscoelastic materials used can cause TASS. TASS may also be due to agents stuck to devices that have become denatured, the wrong concentration of antibiotics used in the Basic Saline Solution (BSS) irrigating solution during intraocular surgery, use of drugs containing preservatives, BSS made up at the wrong pH, or ethylene oxide residue left on plastics. It is recommended that if an outbreak of several cases of TASS occurs, one should investigate the cause and consider stopping similar operative techniques and use of materials. [3, 21] Techniques of instrument cleaning, sterilization, type of water used for cleaning, autoclaving, and the use of reusable instruments and cannulae may need to be investigated. In these circumstances, representative samples should be collected for endotoxin assay from the various potential sources of TASS. Treatment is given with corticosteroids, which can be used aggressively once infection is excluded by making an anterior chamber tap for microscopy and culture and PCR testing if available. [21] Early diagnosis and treatment with a course of topical corticosteroids may yield a good visual prognosis.

10. Management of acute post-operative bacterial endophthalmitis

Evaluation and treatment of acute post-operative bacterial endophthalmitis is initiated when such infection is suspected, generally within few hours of patient's presentation. [1-3] In severe cases, 3-port PPV is recommended depending on the level of visualization. Posterior capsulotomy should be performed and pus and the fibrin material need to be aspirated. Aggressive surgery is not recommended in these circumstances since these eyes may have concomitant retinal vasculitis and edema which may result in retinal breaks and retinal detachment. Following PPV, intra-vitreal antibiotics are injected. [2, 3] Doses of antibiotics are reduced in cases of complete vitrectomy. In addition, intra-vitreal dexamethasone is also injected to reduce inflammation. [3] The procedure can be performed under general, peribulbar, or retro-bulbar anesthesia. General anesthesia may be indicated in cases of severely inflamed eyes. The use of vitrector may be required in cases of infected vitreous. Following the sampling, antibiotics and corticosteroids are injected through the sclerotomy and the sclerotomy incision may not require any suturing.

11. Late-onset post-operative endophthalmitis

Late cases of endophthalmitis after cataract operation are the 2nd most common form of endophthalmitis accounting for up to one-third cases of endophthalmitis. [1, 13] In the late-onset cases of endophthalmitis, the symptoms are milder and Propionibacterium acnes has been reported to be the cause in majority of cases (Figure 7). Because of the difficulty in culturing Propionibacterium acnes and the high rate of recurrence, anterior vitrectomy may be necessary. In these cases, one has to perform capsulectomy to remove the nidus of infection and make the area more accessible for the antibiotic penetration. A further advantage of vi-

trectomy is that adequate material for culturing the causative organism can be obtained besides obtaining of the capsular bag material as well. [3]

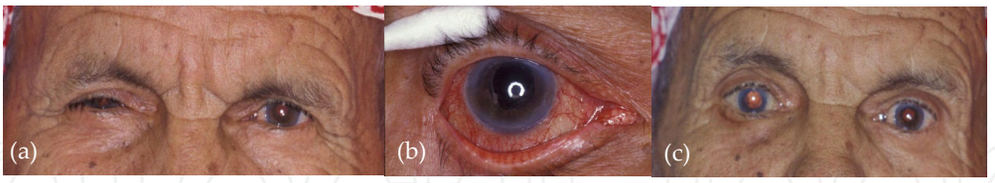

Figure 7. An elderly male patient presented with right eye pain, redness and photophobia (a), which was attributed to delayed onset post-operative endophthalmitis requiring intervention (b). After treatment of intraocular infection, patient's symptoms improved (c).

12. Bleb-related endophthalmitis

Bleb-related endophthalmitis usually follows a chronic course of infection (Figure 8). In these infections, commonest causative organisms are Streptococcus species and Gram-negative bacteria, especially Haemophilus influenzae. [29] Because of the existing history of glaucoma, visual prognosis in these cases is expected to be poor requiring early aggressive intervention. [3] These patients require immediate vitrectomy along with intra-vitreal antibiotic injection. These patients may also require systemic antibiotics. Most frequent causative organisms isolated in cases of delayed-onset bleb-related endophthalmitis include, Streptococcus species, Enterococcus and Gram-negative bacteria. [29] A retrospective consecutive case series of delayed-onset bleb-associated endophthalmitis seen at Bascom Palmer Eye Institute over a 14 year period identified 86 eyes of 85 patients from which 63% eyes were culture-positive. [50] The most common organisms recovered from cultures among these patients were: Streptococcus, 25%; Gram-negative, 18%; coagulase-negative Staphylococcus, 11%; Enterococcus, 7%; Moraxella, 10%; Pseudomonas, 4%; and Serratia, 4%. This large study revealed that culture-positive cases were associated with worse presenting visual acuity, higher presenting intraocular pressure, and worse visual outcomes than culture-negative cases. Streptococcus, Pseudomonas, and Serratia cases were associated with poor presenting view of the fundus and worse visual outcomes than coagulase-negative Staphylococcus and Moraxella cases. [50] Worse view of the fundus in the Streptococcus cases likely compelled the treating clinician to more frequently favor PPV.

13. Endophthalmitis vitrectomy study (EVS)

Endophthalmitis Vitrectomy Study, a multicenter randomized prospective clinical trial of 420 patients with acute post-operative endophthalmitis, showed that immediate PPV provided a clear benefit in a well defined subgroup; patients with light perception vision only at the time of presentation had a significant, 3-fold improved chance of obtaining 20/40 vi-

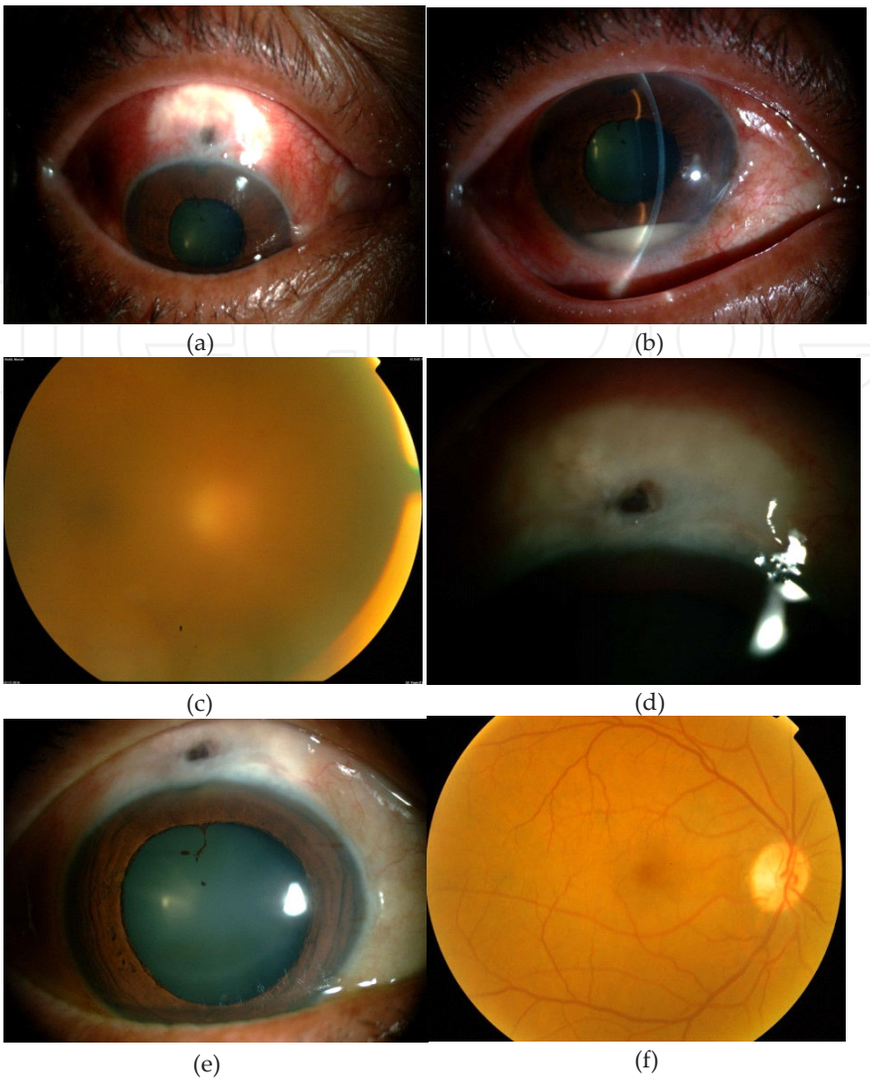

Figure 8. External (a), slit-lamp (b) and fundus (c) photographs of a patient who developed bleb-related endophthalmitis which was treated with topical and intra-vitreal antibiotics resulting in resolution of infection as evident by external (d,e) and fundus photograph (f).

sion or better after PPV. [10] For diabetic patients with hand movement or better vision, at least a trend toward better final VA after PPV was documented compared with vitreous tap and biopsy only. Patients with diabetes had a trend toward worse vision at baseline, higher incidence of positive cultures and need for additional surgeries and worse final visual outcome. [33, 51, 52] According to the EVS recommendations, patients with acute post-operative endophthalmitis after a cataract operation with an initial vision of hand movements or better can be treated by vitreous biopsy and intra-vitreal antibiotics. [10] On the other hand patients having vision at presentation worse than hand movement should undergo immediate PPV. Further, patients with suspected aggressive pathogens such as acute Streptococcal endophthalmitis, immediate PPV may be necessary even though vision is better than light perception at their initial presentation. Immediate PPV can remove the highly inflammatory bacterial pathogens from the vitreous cavity. Retrospective studies have confirmed this no-

tion that affected eyes can benefit from early PPV. Data has shown that there may be difference in how diabetic and non-diabetic patients behave with similar endophthalmitis. [53] Generally, diabetic patients having hand movement or better visual acuity obtain vision of 20/40 more often by PPV than after by only vitreous biopsy and the intra-vitreal injection of antibiotics. Type of infecting organism may have prognostic effect on the final visual outcome. Due to their ability to induce significant inflammation, Staphylococcus aureus, Streptococci, and Gram-negative isolates seem to result in a worse visual outcome. [2, 10] Infections with coagulase-negative Staphylococci had final visual acuity of 20/100 or better in the EVS population (84%). Additionally, 80% cases of culture-negative endophthalmitis resulted in a final visual acuity of 20/100 or better. Other strong predictors for poor visual outcome were initial visual acuity of light perception only, older age, corneal ring ulcers, compromised posterior capsule, abnormal intraocular pressure, presence of RAPD, rubeosis iridis, and absence of the red fundus reflex. [51] Benefits of vitrectomy include a better sample for cultures, reduction of pathogen load, toxins and inflammatory material.

14. Limitations of EVS

The EVS study recommendations do not apply to late-onset post-operative endophthalmitis, bleb-related endophthalmitis, post-traumatic endophthalmitis and endogenous endophthalmitis. [7, 52] In these circumstances and in the absence of any prospective studies, careful evaluation of each case may be recommended by the treating ophthalmologist. Generally, endophthalmitis in these cases may have more aggressive set of bacterial pathogens and therefore require vitrectomy along with intra-vitreal as well as systemic antibiotics. Although, the principles of management in cases of post-traumatic and endogenous endophthalmitis may be the same as for acute post-operative endophthalmitis, the visual outcome is usually dismal.

15. Endophthalmitis associated with microbial keratitis

Many cases of infectious keratitis may progress to endophthalmitis if not treated early in the course of the diseases. [4, 9] Patient with underlying conditions may have propensity to poor response to non-aggressive treatment of infectious keratitis. Infections due to some pathogens may be very difficult to treat in patients with diabetes and other systemic conditions (Figure 9). Patients with chronic diseases, past history of corneal trauma, cataract surgery with lack of posterior capsule, having used topical corticosteroids, compromised immune system and trachoma have a poor visual prognosis. The bacterial species include Mycobacterium chelonae, Nocardia species, Staphylococcus aureus, streptococci and Coliforms as well as Capnocytophaga. [3] In these patients, fungi are the most frequently reported organisms, of which Fusarium species are the commonest. Management in these patients

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may require early intervention that includes intra-vitreal antibiotics guided by the organisms seen on Gram and Ziehl-Neelsen stains of anterior chamber and vitreal taps.

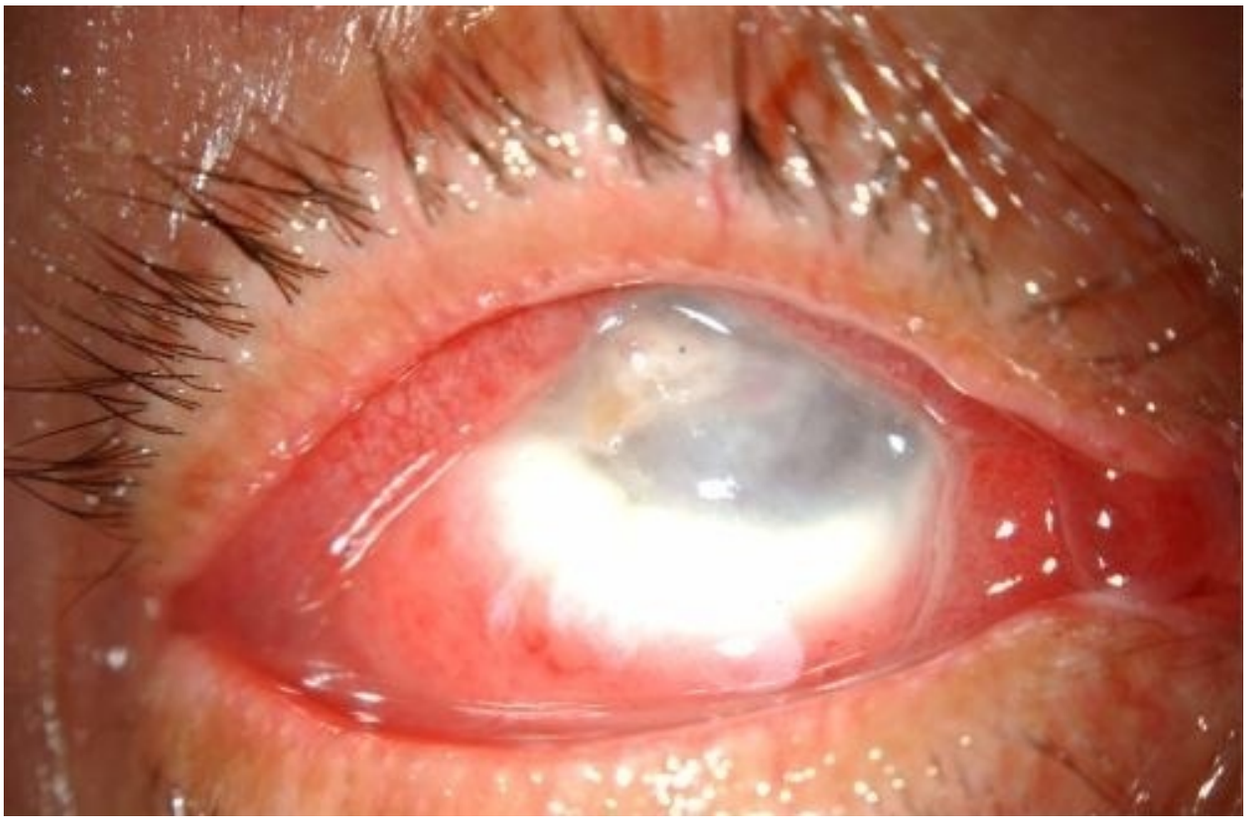

Figure 9. External photograph of a 55-years-old male patient who presented with corneal ulcer which progressed to endophthalmitis despite aggressive medical management.

16. Post-operative endophthalmitis: treatment

According to the EVS, 38% of eyes with post-operative endophthalmitis demonstrated Gram-positive cocci. [10] Since systemically administered antibiotics do not reach sufficient concentrations in vitreous, intravitreal injections have become the accepted primary route of delivery biotic delivery. Desired therapy includes antibiotics which cover most common Gram-positive organisms as well as Gram-negative bacteria. Current protocol includes Gram positive coverage by Vancomycin (1.0 mg/0.1 mL) along with Gram-negative coverage by Ceftazidime (2.25 mg/0.1 mL). If indicated, alternative drugs such as Amikacin (400 ug/0.1 mL), might be considered instead of Ceftazidime. In recent years sensitivity of Gram-negative bacterial species has decreased to the administered Amikacin or Ceftazidime. Potential alternate of Amikacin and Ceftazidime may include 3rd and 4th generation fluoroquinolones, such as Levofloxacin and Moxifloxacin, with their enhanced activity against Gram-positive pathogens having broad-spectrum activity that covers most organisms encountered in bacterial endophthalmitis. [54] Anterior chamber levels achieved using

Moxifloxacin may be higher than those obtained with any other topically administered fluoroquinolone antibiotics, however, these levels are too low for effective treatment of intraocular infections. [55]

Depending on the pharmacokinetics of the drugs selected, intra-vitreal antibiotics may be repeated as needed according to the clinical response at intervals of 48 to 72 hours. The doses selected needs to be appropriate to prevent retinal toxicity. In cases of total vitrectomy, the doses of the intra-vitreal antibiotics are reduced. According to the EVS, systemic antibiotics do not appear to have any effect on the course and outcome of endophthalmitis after cataract surgery. [10] Vancomycin provides a good coverage for Gram-positive bacteria including Methicillin-resistant Staphylococcus aureus. While, Ceftazidime provides a good coverage for Gram-negative bacteria, Clindamycin, Vancomycin, or Cefuroxime are effective for Propionibacterium acnes endophthalmitis. [3] Anti-inflammatory therapy in the form of corticosteroids at the time of intra-vitreal antibiotics can limit the tissue destruction by infiltrating leukocytes due to their cytokines. Intra-vitreal Dexamethasone injection (400 mg/0.1 mL) after vitrectomy may lead to a rapid subsidence of the intraocular inflammation. [3]

17. Post traumatic endophthalmitis

The incidence of endophthalmitis after open globe injuries ranges between 2-17% of cases depending on the design of the study and geographical location. [31] For example, a major collective review of 4795 post-traumatic eyes evaluated in 15 tertiary care centers in China over a 5 years period revealed an incidence of 8.4%. [56] In cases of initial evaluation of post-traumatic endophthalmitis, one must exclude presence of an IOFB, as in cases of IOFB, there is much greater risk of developing endophthalmitis than in cases where no IOFB is involved. The incidence of endophthalmitis associated with IOFB may be even higher in the setting of having a ruptured globe in the rural areas as compared with trauma in the urban setting (Figure 10). In the rural areas, the occurrence of post-traumatic endophthalmitis may be as high as 80% after an injury. In contrast, post-traumatic endophthalmitis occurred in 11% of 204 patients in non-rural districts. Depending on the virulent nature of the infecting organism, post-traumatic endophthalmitis may occur within hours or several weeks after trauma. [57] In these eyes, the signs of infection usually occur early but may be masked by the post-traumatic reactions of the injured tissue. [58] The initial symptoms are usually pain, intraocular inflammation, hypopyon, and vitreous clouding. Risk factors for endophthalmitis after ocular trauma include, delayed presentation, older age, unclean wound, lens capsule rupture and the presence of IOFB. [31, 57, 59] Appropriate history should be obtained regarding the setting of the trauma and likely nature of the IOFB present. When the fundus view is not possible, imaging studies in the form of ultrasonography and computed tomography should be requested. Magnetic resonance imaging is avoided in cases of suspected metallic IOFBs. Without an imaging study, the IOFB can be missed. To save vision, the IOFB needs prompt removal along-with intra-vitreal antibiotics injections.

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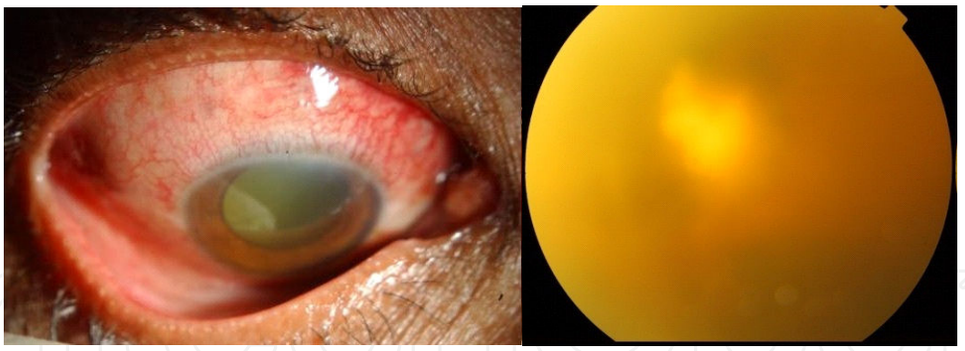
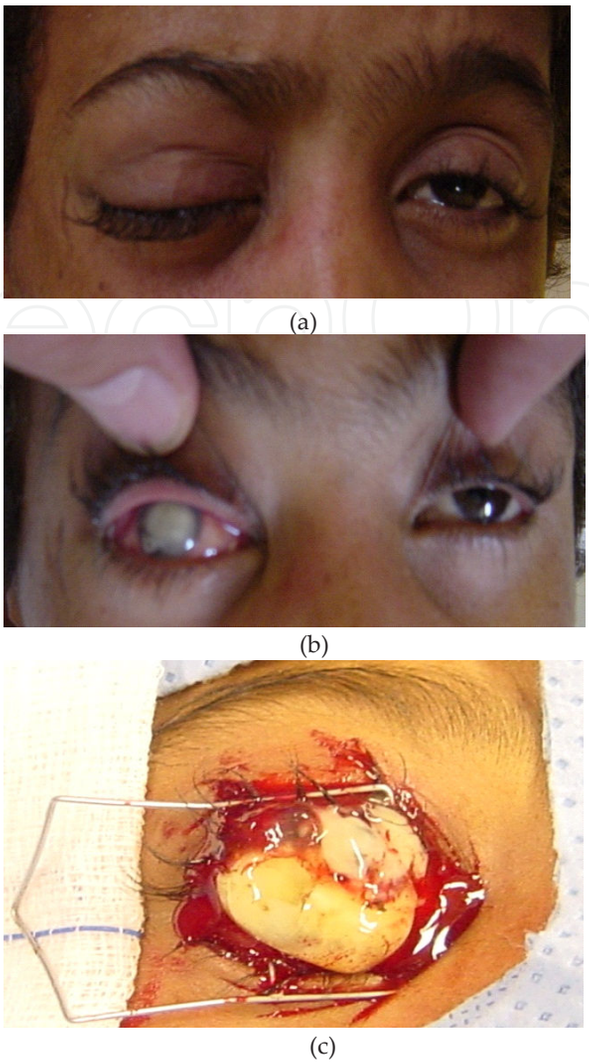


(a) (b)

Figure 10. External photograph of a 63-years-old patient who presented with decreased vision, redness, tearing and pain in his right eye after having trauma several days earlier (a). He was found to have cloudy vitreous and no clear view of the fundus (b). A diagnosis of endophthalmitis was made and patient was treated with intra-vitreal antibiotics after obtaining vitreous biopsy.

Similar to post-operative endophthalmitis, two thirds of the bacteria in post-traumatic endophthalmitis are Gram-positive and 10% to 15% are Gram-negative. [31] In contrast to post-operative endophthalmitis, virulent Bacillus species are the commonest pathogens in post-traumatic endophthalmitis and can be present in 20% of all cases. In the rural population, they are also found in 42% of cases of post-traumatic endophthalmitis. They are thus the second commonest cause of all cases of endophthalmitis. Most Bacillus infections are associated with IOFB. Infections that are caused by Bacillus species usually commence with rapid loss of vision together with severe pain (Figure 11). Bacillus species are resistant to Penicillin and Cephalosporins, but are sensitive to Gentamicin and Vancomycin. Other bacteria include Staphylococcus species, Streptococci, Coliforms, and Clostridium species. [1, 6] Fungi are the causative organisms in 10% to 15% of cases of endophthalmitis after trauma and may occur weeks to months after the trauma. [13]Although mixed microbial infections tend to be less common in post-operative cases of endophthalmitis, they have been isolated in up-to 42% of the trauma-associated endophthalmitis. [1-3]

As compared to post-operative endophthalmitis, the prognosis of post-traumatic endophthalmitis is usually poor. [28, 31] Poor prognosis stems from the presence of more virulent pathogens, presence of mixed infections, traumatic tissue injury and the failure to start prophylactic antibiotics. Microbiologic spectrum and visual outcome of culture-positive cases of infectious endophthalmitis after open globe injuries have been presented from two tertiary eye care centers in the Middle East by Al-Omran et al. [59] The most common isolates were coagulase-negative staphylococci and Streptococcus species (26.9% of isolates each). Gram-negative organisms and fungi comprised 12.8% and 3.8% of isolates, respectively. The most common organisms identified were coagulase-negative staphylococci and Streptococcus species. Clinical features associated with better visual acuity outcomes included better presenting visual acuity, early presentation to the eye clinics, and isolation of a nonvirulent organism. Post-traumatic endophthalmitis is associated with a poor visual prognosis.



(a)

(b)

(c)

Figure 11. External photographs of a 13-years-old male who presented one week after trauma to his right eye (a and b). He was found to have no light perception vision and evidence of pus filled right eye which required evisceration (c).

18. Risks of endophthalmitis with retained IOFB and prevention

Intraocular penetration of a dirty or soil-contaminated foreign body requires an emergent intervention. Delayed removal of IOFB following trauma may result in a significant increase in the development of clinical endophthalmitis. Risk factors for poor visual outcome may include poor initial presenting VA, posterior location of IOFB and the lack of vitrectomy at the time of initial IOFB removal. [27, 28, 59] A retrospective study of a 20-year review found that 8% of patients with an IOFB developed endophthalmitis, of whom half lost all light perception. [1, 6] One of the largest study of penetrating eye trauma and retained IOFB in eyes of 565 patients managed at a large tertiary eye care center over a 22 year period revealed that 7.5% of them developed clinical evidence of endophthalmitis at some point after trauma. [31] In these patients, the initial presenting VA of 20/200 or better was recorded in only 18.1% of eyes and the remaining 81.9% had VA ranging from 20/400 to light perception. On-

ly 25% of these eyes underwent IOFB removal and repair within 24 hours after trauma while 75% had IOFB removal 24 hours or more after trauma. From this group, 70% underwent primary PPV at the time of removal of posteriorly located IOFB and only 38.6% had positive cultures. Improvement in vision was only possible in 47.7% of eyes and 38.7% had deterioration of their vision, including 22.7% that had complete loss of vision. Predictive factors for the good visual outcome in these patients included good initial presenting VA, early surgical intervention to remove IOFB (within 24 hours), and PPV. Predictors of poor visual outcome included IOFB removal 48 hours or later, posterior location and no PPV at the time of initial surgery (Figure 12). [31]

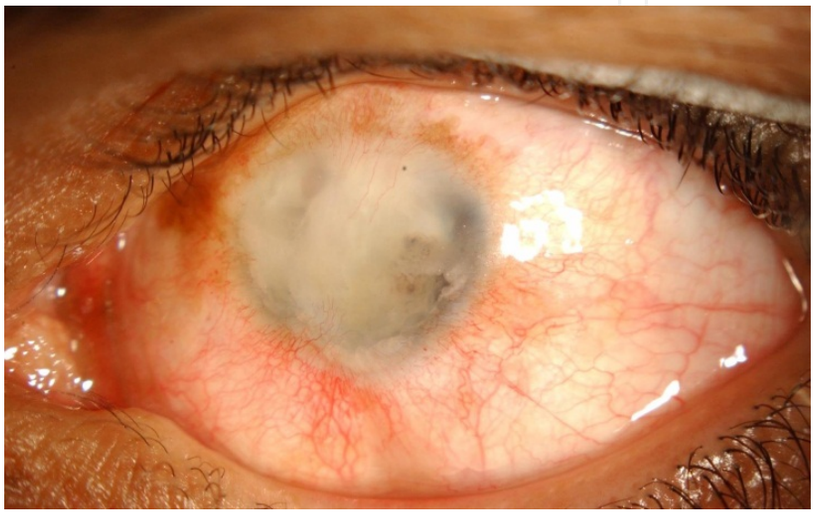


Figure 12. External photograph of a 43-years-old male who developed post-traumatic endopthalmitis resulting in phthisis of his left eye despite aggressive medical and surgical intervention.

Antibiotic prophylaxis has been advocated for IOFB removal. All patients suspecting of an IOFB should require antibiotic prophylaxis. Beside virulent infections caused by Bacillus species in the setting of IOFB which can cause severe visual loss, Staphylococcus aureus, Coliforms, Streptococci, and, sometimes Clostridium perfringens can also cause sight-threatening endophthalmitis. [60] If trauma takes place in a rural area, there is more likelihood of infection to be a polymicrobial infection. [27, 28, 31, 59] If the patient presents early with good vision and the IOFB is recognized and treated as soon as possible, then the chances of endophthalmitis are reduced.

19. Exogenous fungal endophthalmitis

Exogenous fungal endophthalmitis has been reported more often from countries in the tropical region. Most common causes of exogenous fungal endophthalmitis include Aspergillus and Fusarium species. [3] These infections are usually associated with trauma, but can follow intraocular surgery especially in the rural settings. [61] The filamentous fungus especially Aspergillus as well as Fusarium cause infection following trauma with soil contaminated

objects. [61]According to some studies, up to 50% of central corneal ulcers may be caused by fungi and almost 50% of these cases may be associated with fungal endophthalmitis. [62] The fungal endophthalmits can also occur due to the failed treatment of contact lens-associated keratitis. Exogenous fungal endophthalmitis is mostly sight threatening unless aggressive intervention by antifungal therapy and surgery initiated. Effective therapy requires proper identification of the causative organisms and their sensitivity to the desired antifungal agents (Figure 13). Currently, some of the effective antifungal drugs include Amphotericin B, Natamycin, Flucytosine, Thiabendazole, Miconazole, Ketoconazole, Clotrimazole, Econazole, Fluconazole, Itraconazole, Voriconazole, and Posaconazole. Amphotericin B is the only fungicidal depending on concentration achieved, and is active against a wide range of fungi including Aspergillus species, Fusarium species and Candida species. It may be given topically, sub-conjunctivaly, and intra-vitreally. [63] In addition to intra-vitreal therapy, Amphotericin B is given systemically by a slow intravenous infusion for the treatment of fungal endophthalmitis. For fungal endophthalmitis, Amphotericin or Miconazole is usually used following vitrectomy. Amphotericin B can be administered intravenously combined with oral Flucytosine for severe Candida endophthalmitis associated with retino-choroiditis. For Candida retinochoroiditis without endophthalmitis, treatment is effective with systemic Ketoconazole, Fluconazole, or Voriconazole. [64]

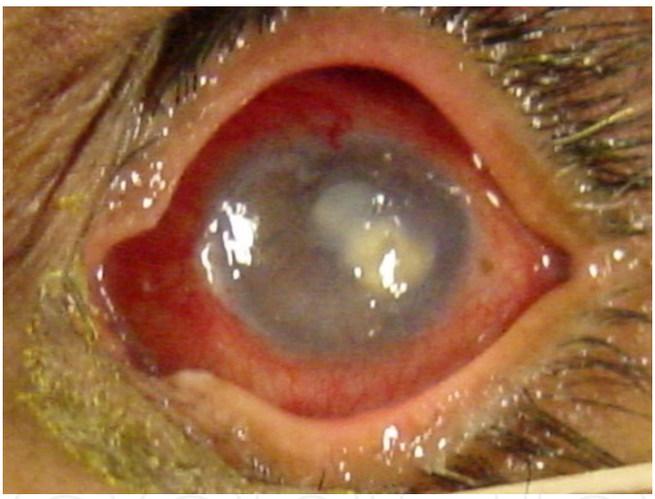


Figure 13. External photograph of left eye of an elderly female who developed fungal keratitis and endophthalmitis requiring surgical as well as systemic antifungal treatment.

Treatment for minimal fungal chorioretinitis and vitritis include systemic antifungal therapy along with serial ophthalmic evaluations. [3, 61, 64] In cases of moderate to severe vitritis due to fungal endophthalmitis, intra-ocular antifungal therapy along-with systemic as well as surgical intervention may be necessary to treat fungal endophthalmitis (Figure 14). Recommended treatment protocols include, Amphotericin B and Voriconazole as primary therapeutic options. [61, 64] Both can be given systemically and intra-vitreally. Since the intraocular penetration of Amphotericin B after topical or systemic treatment is limited, and many fungal pathogens are not susceptible to these agents, Voriconazole seem to be promising alternative. Systemically administrated Voriconazole has a good intraocular penetration

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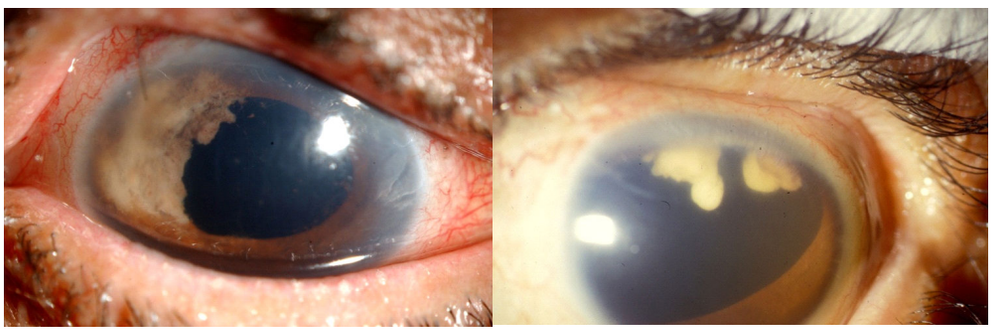
with minimal systemic side effect profile as compared with amphotericin B. In general in vitro susceptibility of Candida, Aspergillus, and Fusarium species appears to be almost 100% to the administered Voriconazole. [63] Candida endophthalmitis seems to result in better outcome than Aspergillus endoophthalmitis. Caspofungin appears to have a very good activity against Candida and Aspergillus species and when administered systemically along with Voriconazole, it has been found to be very effective in treating endophthalmitis caused by these organisms. Due to its unique mechanism of action and high activity against yeast and molds, Caspofungin may show more promise in future treatment strategies for fungal endophthalmitis. Fusarium endophthalmitis is particularly difficult to treat, requiring both surgical removal of the inoculums along with Amphotericin and Imidazoles therapy. Generally, Voriconazole or Fluconazole (to cover Candida albicans) or Itraconazole (to cover other Candida species, Aspergillus or Cryptococcus) can be considered. [65, 66]



(a) (b)

Figure 14. Post-operative delayed fungal endophthalmitis; photograph (a) showing sectoral iris infiltration with Aspergillus niger requiring pars-plana vitrectomy, total capsulectomy, total iridectomy and removal of intraocular lens, photograph (b) showing white plaque extending from the upper capsule equator caused by Aspergillus terreus requiring 3 PPVs and intra-viteal Amphotericin B injections and eventual enucleation because of recurrent fungal infection. (Figures reproduced with permission: Al-Mezaine HS, Al-Assiri A, Al-Rajhi AA. Incidence, clinical features, causative organisms, and visual outcomes of delayed-onset pseudophakic endophthalmitis. Eur J Ophthalmol 2009;19:804-811).

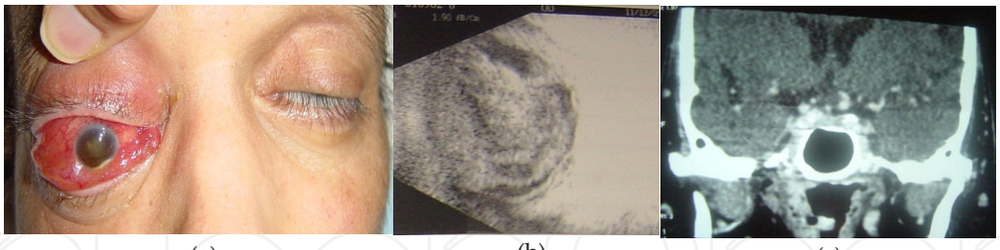
20. Endogenous endophthalmitis

Endogenous endophthalmitis is a severe vision-threatening intraocular infection that spreads through bloodstream from a concurrent infection somewhere else in the body. Endogenous endophthalmitis is relatively uncommon, accounting for 2% to 8% of all reported cases of endophthalmitis. [67] The outcome of endogenous bacterial endophthalmitis has not improved over the last several decades and clinicians need to have a high level of suspicion of this commonly misdiagnosed condition. [67, 68] The majority of patients with endogenous endophthalmitis are initially misdiagnosed and many have an underlying disease known to predispose to infection. Blood cultures may be the most frequent means for establishing the infective cause. Endogenous bacterial endophthalmitis usually leads to total loss of vision. Although most cases of endogenous endophthalmitis present as unilateral, bilateral cases have also been reported. [69, 70] In a large study of endophthalmitis from a major center over a 10-

year period, 86 cases were reported; 10 of these were due to endogenous causes. [71] The poor visual outcome in these patients has been related to the delay in the early diagnosis and appropriate timely treatment. [72] Systemic symptoms rather than acute ocular symptoms may be the most common reasons for a patient to present to a physician and many of these cases may be initially misdiagnosed. Jackson et al. reviewed 267 reported cases of endogenous bacterial endophthalmitis and also presented a 17-year prospective series. [67]

21. Risk factors for endogenous endophthalmitis

The most frequent risk factors for developing endogenous endophthalmitis include a prior history of diabetes mellitus, gastrointestinal disorders, hypertension, heart valve diseases, endocarditis, chronic obstructive lung disease, previous wound infection, meningitis, urinary tract infection, cystic fibrosis, immune-compromised status, splenectomy, organ transplantation and indwelling intravenous catheters, hepatic abscess, hemodialysis fistula, peritonitis and intravenous drug abuse (Figure 15). [71-78] Less frequent risk factors include, otitis media, dental infection, septic arthritis, abortion, pharyngitis and Hemoglobin SC disease. [79-83] Other chronic diseases such as immunosuppressive status, HIV infection, cancer, renal failure requiring dialysis, long-term use of broad-spectrum antibiotics, use of steroids and other immunosuppressive drugs, intravenous hyper-alimentation and indwelling intravenous catheters can lead potential pathogens access to the circulatory system and septicemia. History of chronic intravenous drug abuse, dental work, otitis media, soft-tissue infection including orbital cellulitis, and septic arthritis may lead to septicemia and endogenous endophthalmitis. [3, 79, 80]



(a) (b) (c)

Figure 15. External photograph of a diabetic patient who presented with loss of vision and painful ophthalmoplegia of his right eye along with fever and mental status changes (a). He was found to have severe panophthlamia of his right eye and ultrasonography revealed endophthalmitis (b). Computed tomography (coronal view) of his brain revealed evidence of septic emboli (c). Patient was treated with systemic antibiotics and right eye evisceration.

22. Endogenous endophthalmitis: presenting features and diagnosis

New onset of floaters, blurred vision, photophobia and ocular discomfort in a patient with underlying systemic risk factors may be the presenting features of endogenous endophthalmitis. Clinical findings in endogenous endophthalmitis may include decreased VA, ocular

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pain, conjunctival injection, hypopyon, corneal edema, vitritis and reduced fundus view (Figure 16). Endogenous bacterial endophthalmitis is bilateral in approximately 14- 25% of cases. In bilateral infection, simultaneous ocular involvement is the rule; however, one eye is characteristically more severely affected than the other eye. Delayed involvement of the second eye can occur even in patients already being treated with systemic antibiotics. The right eye is involved twice as often as the left, probably because of this eye's proximity and more direct blood flow from the right carotid artery. There is no gender predisposition in cases of endogenous endophthalmitis. For prognostic purposes, endogenous endophthalmitis has been classified based on location (anterior or posterior) and extent (focal or diffuse). [72] According to this classification, focal and anterior cases appear to have a good prognosis, while posterior and diffuse endophthalmitis nearly always leads to blindness. In panophthalmitis, severe involvement of both the anterior and posterior segment is associated with inflammation of orbital structures, indicated by marked eyelid edema, chemosis, proptosis and limitation of eye movements. Ultrasonography may be helpful in the diagnosis; the combination of thickening of the retinochoroid layer and echoes in the vitreous supports the diagnosis of endophthalmitis. [72, 84] On MRI of the orbits, intra-ocular hyperintensity on fluid-attenuated inversion recovery and diffusion-weighted images have been found to be very useful for diagnosing endophthalmitis. [85] No eyes that have suffered posterior, diffuse or panophthalmitis has received any useful vision regardless of management. [7] Pathological examination of the enucleated globes in panophthalmitis has revealed that most of the retina is necrotic resulting in devastating visual outcome. [72]

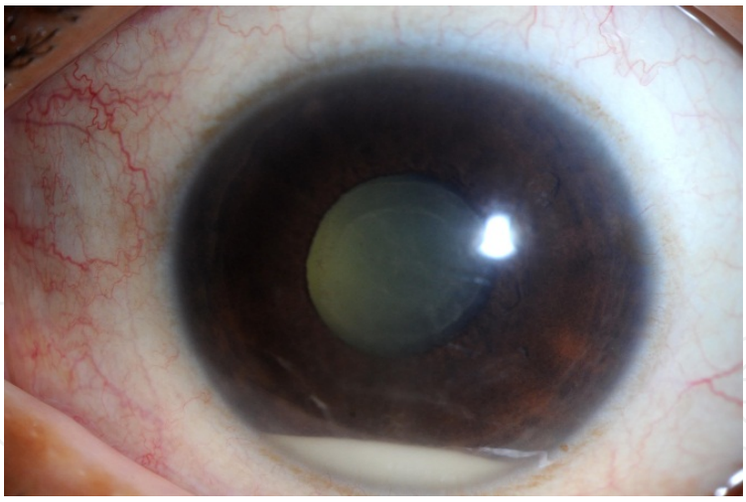
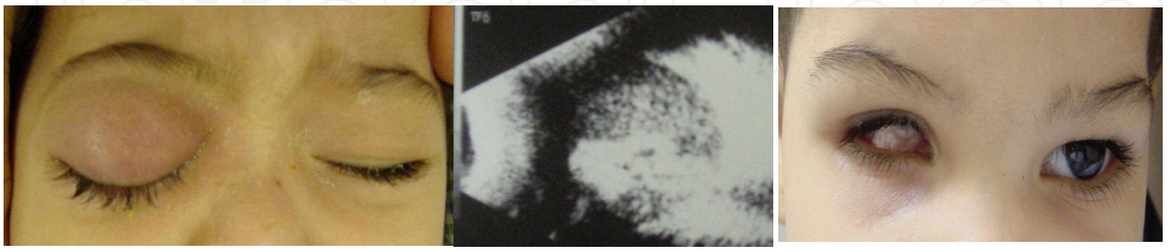


Figure 16. External photograph of a patient's eye who presented with pain, conjunctival chemosis and decreased vision. His examination was significant for having an evidence of anterior chamber reaction in the form of hypopyon and vitritis. A diagnosis of endogenous endophthalmitis was made in the absence of patient's having no prior history of ocular trauma or surgery.

The majority of patients with endogenous endophthalmitis are initially misdiagnosed and many have an underlying systemic diseases frequently overlooked by ophthalmologists (Figure 17). Blood cultures may be the most frequent means for establishing the infective cause. If not diagnosed early on and therapy initiated, endogenous bacterial endophthalmi-

tis usually leads to total loss of vision. [7] In Candida infections, localized fluffy creamy white retinal or sub-retinal nodules may be associated with vitreous haze. [82, 83] In advanced cases of fungal endogenous endophthalmitis, one may encounter areas of peri-vascular infiltrates, retinal infarction, hemorrhages and retinal necrosis. Patients having evidence of systemic fungal infection need to be screened for any peripherally located fungal lesions as these patients may be asymptomatic initially.



(a) (b) (c)

Figure 17. External photograph of a child who presented with gradual swelling of his right eyelids, pain and loss of vision over one month period after a bout of gastrointestinal illness. There was no prior history of eye trauma or surgery (a). Based on ultrasonography (b), a diagnosis of panophthalmitis was made and the child was treated with intravitreal antibiotic injection after obtaining vitreous biopsy to which patient responded well. Culture results revealed evidence of Enterococcus faecalis and the eye became rapidly phthisical (c).

Early diagnosis of endogenous endophthalmitis can be suspected only if there are ocular symptoms associated with concomitant systemic infection. [86] While in adults, early ocular symptoms may prompt patients to see an ophthalmologist and perhaps endogenous endophthalmitis diagnosed and treated early in the course, in cases of pediatric endogenous endophthalmitis delay in early diagnosis and treatment may result in no light perception vision or loss of an eye. [7, 87] The earliest symptoms of adult endogenous endophthalmitis include pain and decreased vision. However, because of poor communication in pediatric patients diagnosing endogenous endophthalmitis at an early stage is very difficult. Unfortunately, in pediatric patients endogenous endophthalmitis is often not suspected and may be even misdiagnosed as uveitis, persistent hyperplastic primary vitreous, cataract, retinopathy of prematurity, Toxocariasis, Coat's disease, retinal detachment and retinoblastoma. [7, 72]

Patients suspected of having endogenous endophthalmitis require immediate investigation with blood cultures along with anterior chamber and vitreous taps and possibly vitrectomy along with intravitreal antibiotic injections. [88] Gram stain of the specimens along with cultures and sensitivity as well as PCR if possible should be performed. Isolation of any bacterial colonies on direct inoculation of agar plates cultured aerobically or anaerobically may be indicative of culture-positive endophthalmitis. Blood cultures may be the most frequent means for establishing the infective cause. Identification of the causative pathogen by blood, urine, or cerebrospinal fluid culture may be successful in over 75% of endogenous endophthalmitis cases. Positive cultures from vitreous samples can be achieved much less frequently in endogenous endophthalmitis than in exogenous endophthalmitis. [3, 67, 71, 72] Vitrectomy has the advantage of obtaining material for cytologic and microbiologic studies

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to make the correct diagnosis and allowing removal of the offending organisms. Vitreous specimens for culture obtained by vitrectomy have been found to be more sensitive in detecting the causative organism than the vitreous needle biopsy. [88, 89] In some cases, the culture of the vitreous samples may not grow any bacteria probably due to effect of antibiotics. Vitreous biopsy should be considered because a culture of the vitreous sample is useful for identifying the responsible bacteria. The positive rate for identification of any causative organism may be 87% for vitreous, 32% for aqueous humor, and 33% for blood. In addition to cultures, in certain cases and for fastidious organisms, bacterial and fungal DNA can be detected by PCR assay in specimens obtained from the ocular tissues. [90 -92] DNA extracted using a single-extraction protocol from 50 microL of vitreous and amplified with broad-range bacterial and fungal primers (targeting the conserved 16S and 18S ribosomal RNA gene sequences of bacteria and fungi, respectively) may enable the rapid differentiation between bacterial and fungal endophthalmitis and allow tailoring of therapy to individual patients. [91, 93] RNA-based Reverse Transcriptase PCR (RT-PCR) can be utilized to confirm presence of viable bacteria in intraocular specimens obtained from patients with infectious endophthalmitis. RT-PCR can serve as a rapid and reliable tool to detect viable bacteria causing endophthalmitis. [20]

23. Bacteriology of endogenous endophthalmitis

Depending on location, a wide range of organisms have been shown to cause endogenous endophthalmitis. Causative organisms of endogenous endophthalmitis may be bacteria, as well as fungi, which vary depending on the geographical location. For example in Europe and the United States, Streptococcus species, Staphylococcus 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. [71, 82] These numbers differ significantly from East Asia, where most cases of endogenous endophthalmitis are caused by Gram-negative organisms especially Klebsiella species accounting for 80% to 90% of positive cultures. [67, 94] The difference might be associated with higher incidence of cholangio-hepatitis and liver abscess in these patients. Some of the other reported organisms include, Candida albicans, Neisseria meningitis, Enterococcus, Haemophilus influenzae, Klebsiella, Salmonella, Streptococcus, Staphylococcus aureus, Escherichia coli, Kingella Kingae, Pseudomonas aeroginosa, Propionibacterium acnes, Serratia, Bacillus cereus, Brucella melitensis and Actinobacillus. [67, 71-73, 77, 78, 81, 84, 95-98] Studies from East Asian countries have reported liver abscess as the major source of infection and Klebsiella pneumoniae as the causative organism. [81, 94] Incidence of fungal endogenous endophthalmitis has increased in recent years, Candida albicans and Aspergillus species being the prominent causative agents. Candida species are the most common cause of nosocomial fungal infections in compromised hosts. Candida chorioretinitis occur predominantly as a result of candidemia seeding the eye. Cryptococcus and Fusarium species have also been reported to the cause of endogenous fungal endophthalmitis. Compared with published series of post-operative or post-traumatic endophthalmitis, patients with endogenous endophthalmitis are more likely

to have fungal isolates with a predominance of Candida albicans. The most common Gram positive organisms are Staphylococcus aureus, group B streptococci, Streptococcus pneumoniae,and Listeria monocytogenes; the most common Gram negative organisms are Klebsiella spp., Escherichia coli, Salmonella, Pseudomonas aeruginosa, and Neisseria meningitidis. [2, 3, 69, 91]

24. Management of endogenous endophthalmitis

The optimal treatment for endogenous endophthalmitis is controversial. When indicated, these patients may require systemic antibiotics in addition to the PPV. While EVS has provided guidelines for the role of early vitrectomy and intra-vitreal antibiotics in post-operative endophthalmitis, no such study has addressed endogenous endophthalmitis. Data from the EVS may not be applicable to cases of endogenous endophthalmitis because the spectrum of causative organisms differs significantly in endogenous endophthalmitis as compared to post-operative endophthalmitis. Although systemic and intra-vitreal antibiotics may be sufficient in milder forms of infection, PPV has been shown to be helpful in severe cases of endogenous endophthalmitis. More virulent organisms such as endotoxin-producing Streptococcus and Bacillus species are commonly involved in endogenous endopthalmitis. [67, 71] In addition, material from vitrectomy may provide a better source for culture. This is particularly true in children because of the variety of pediatric cases and lack of sufficient experience in diagnosing in this age group. [7] In the adults, early intervention with PPV has been found to be highly effective, no such data has been proven for cases of pediatric endogenous endophthalmitis. Suggested medical treatment in these patients include topical, sub-conjunctival and intra-vitreal injection of antibiotics having broad coverage with consideration for corticosteroids in cases of severe inflammation. Patients with endogenous endophthalmitis should be evaluated for underlying systemic conditions. Systemic anti-microbial therapy is the mainstay of endogenous endophthalmitis. Intravitreal antibiotic selection is similar to exogenous endophthalmitis including Vancomycin (1.0 mg/0.1 mL) for Gram-positive coverage or in combination with Ceftazidime (2.25 mg/0.1 mL) or Amikacin (400 ug/0.1 mL) for Gram-negative coverage.. In general, systemic therapy must be continued for several weeks to ensure eradication of the infection. Generally, a combination of intra-vitreal antibiotics is injected that may include Vancomycin, Cephazolin or Ceftazidime and Amikacin after the tap has been performed. Systemic antibiotics are administered according to the focus of the infection. Infectious diseases consultation may be sought in cases of endocarditis and early vitrectomy should be planned if indicated. [88] Immediate vitrectomy is performed in eyes with light-perception-only vision at the initial visit. Routine immediate vitrectomy is not necessary in eyes presenting with better than light-perception vision. Aggressive therapy and early vitrectomy may be considered in endogenous endophthalmitis caused by virulent pathogens such Pseudomonas aeruginosa and in cases of Klebsiella endophthalmitis. [81, 97, 99] Patients with endogenous endophthalmitis who undergo PPV early in the course of endogenous endophthalmitis may end up with some useful vision.

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25. Visual outcome in endogenous endophthalmitis

Endogenous endophthalmitis is generally associated with high mortality and poor visual outcomes, particularly when caused by more virulent species such as Aspergillus. [98] Fungal endopthalmitis has a poor visual outcome as compared to bacterial endophthalmitis. [100] The visual outcome in cases of treated Streptococcal endophthalmitis is generally poor than some of the Staphylococcal species. Patients with good initial VA typically have good final VA. It is believed that an active therapeutic approach including intra-vitreal antibiotics and vitreo-retinal surgery may save eyes from blindness. In the past, the visual outcome has been poor with most cases leading to blindness in the affected eye. [70, 81] In an experimentally model of endogenous endophthalmitis, infant rats inoculated by either intra-nasal or intra-peritoneal injection of Haemophilus influenzae type b, suppurative endophthalmitis occurred in 50% of bacteremic animals who survived. [101] This experimental induced endogenous endophthalmitis ultimately progressed to panophthalmitis followed by organization of the exudate and phthisis bulbi. Recent data for the effectiveness of vitrectomy and intra-vitreal antibiotics to save some vision has been encouraging. [88] Endophthalmitis due to Streptococcal species may result in earlier onset and perhaps worse visual outcome. On the other hand, endophthalmitis which yields no positive results from culture usually have delayed onset of infection and better visual results.

26. Endogenous fungal endophthalmitis

In fungal endophthalmitis, some of the most important metastatic sources of infections include endocarditis, gastrointestinal tract, genitourinary tract, skin wound infections, pulmonary infections, meningitis, and septic arthritis. [102] Other predisposing factors include chronic invasive procedures, such as hemodialysis, bladder catheterization, total parenteral nutrition, chemotherapy, dental procedures, and intravenous drug abuse (Figure 18). In the past, the incidence of endogenous fungal endophthalmitis has been estimated to range between 9- 45% of patients with disseminated fungus infection which has decreased in recent years to less than 3%. [1, 102] Candida albicans is by far the most frequent cause (75-80% of fungal cases), followed by Aspergillus species. Because of advanced medical care and a longer life-span of patients with chronic diseases in the Western countries along with frequent use of long-term intravenous access, Candida albicans retino-choroiditis has become more common in clinical practice and less common in those with organ transplants and immunosuppression as the result of early ophthalmological screening of all susceptible patients. [81, 99] Endophthalmitis may occur in patients with candidemia depending on the population studied, especially those with an organ transplant and having a highly immunocompromised status. [1, 3] Aspergillosis is the second most common cause of fungal endophthalmitis, particularly in intravenous drug abusers. Less frequent causes are other Candida species, Torulopsis glabrata, Cryptococcus neoformans, Sporothrix schenckii, Scedosporium apiospermum (Pseudallescheria boydii), Blastomyces dermatitidis, Coccidioides immitis, and Mucor.

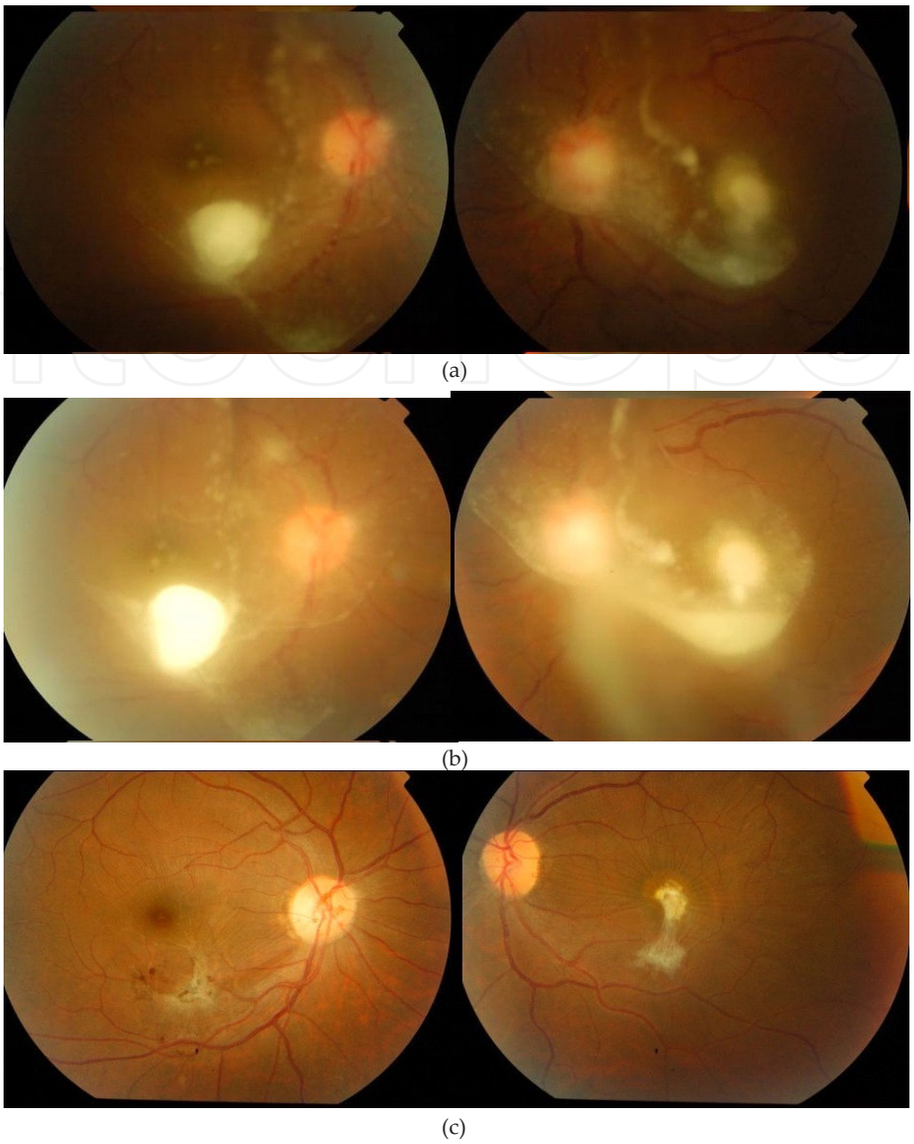

Figure 18. Fundus photographs of a 35-years-old immuno-compromised male patient who presented with bilateral decreased vision. He was found to have evidence of bilateral fungal endophthalmitis (a). Initially the patient was treated by intra-vitreal antifungal agents (b). Because of worsening of infection, bilateral pars-plana vitrectomy along-with systemic antifungal therapy resulted in clearance o f his eye infection (c). (Photographs: Curtsy of Essam Al-Harthi, MD).

27. Orbital and peri-orbital cellulitis as a cause of endogenous endophthalmitis

Orbital and peri-orbital cellulitis have been reported as causes of endogenous endophthalmitis. [8, 37] Facial cellulitis is rarely reported as a focus of infection leading to endogenous endophthalmitis. Facial cellulitis usually appears more rapidly than other deep infections, so treatment is required early on. However, facial cellulitis can be a direct or indirect causa-

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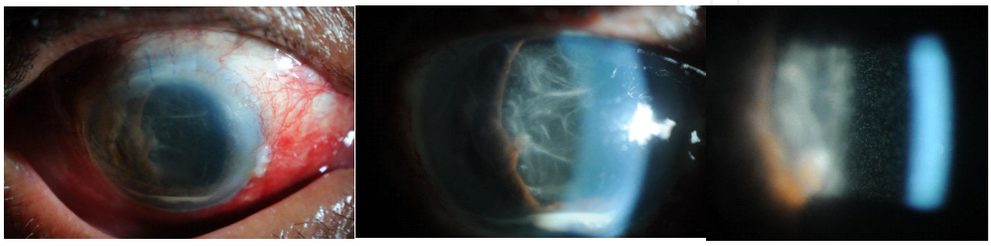
tive infection. The indirect pathway involves distant spread through the blood stream via the internal jugular vein. Microorganisms are then able to spread through the heart to the internal carotid artery and ophthalmic artery. Furthermore, they can follow a retrograde pathway toward the cavernous sinus of the skull, establishing thrombophlebitis in the facial vessels. These anatomical characteristics explain how facial cellulitis can be a primary infection site of endogenous endophthalmitis. Kang et al, [8] reported a case of 51-year-old unconscious woman presenting with fever, facial swelling, and decreased VA secondary to facial cellulitis, endogenous endophthalmitis and end-stage renal disease. These authors reported successful treatment with intra-vitreal (Vancomycin, Ceftazidime) and intravenous antibiotics (Vancomycin, Meropenem). The authors reported a successful outcome in their patient's bilateral endogenous endophthalmitis following timely treatment with the intra-vitreal as well as systemic antibiotic administration.

28. Endophthalmitis after intra-vitreal injections

In recent years, increasing number of iatrogenic cases of endophthalmitis have been reported as a result of increased used of intra-vitreal injections for various retinal conditions. [103-108] Studies have suggested that coagulase-negative Staphylococci, like postoperative endophthalmitis, appear to be the predominant organism in the pathogenesis in the development of endophthalmitis after intra-vitreal injection. Variety of other organisms have been implicated in the development of endophthalmitis following intra-vitreal injections of anti-VEGF agents as well as intra-vitreal Triamcinolone injections (Figure 19). Alkuraya et al, [106] reported a case of culture-positive endophthalmitis after intra-vitreal injection of bevacizumab (Avastin) in a 51-year-old diabetic women. In their case, the patient presented with decreased vision, redness, and mild pain in her eye 3 days after intra-vitreal injection of Avastin for macular edema due to a branch retinal vein occlusion. A clinical diagnosis of endophthalmitis was made, a vitreous tap was performed and intra-vitreal antibiotics were administered. Because of worsening of the endophthalmitis, PPV was undertaken followed by repeat intra-vitreal antibiotic injection. The patient's ocular condition improved dramatically; however, her VA did not improve. The cultures from vitreous taps revealed Staphylococcus lugdunesis. An up-to-date overview of all patients reported in the literature with



(a) (b) (c)

Figure 19. External (a) and slit-lamp (b,c) photographs of a patient's eye who developed endopthalmitis after intraviteal Triamcinolone injection to treat post-operative macular edema.

suspected bacterial endophthalmitis along-with specific symptoms and signs which could differentiate between infectious and non-infectious causes following anti-VEGF injection has been reported by Hoevenaars et al. [108] These authors reviewed case series of 118 patients from the PubMed data along with records of their own 15 patients from the Rotterdam Eye Hospital with suspected bacterial endophthalmitis after anti-VEGF injection. Their study revealed that patients presenting with a VA of 20/200 (logMAR 1.0) or less and later than 24 hours after injection were more likely to have bacterial endophthalmitis and suggested that in order to prevent under-treatment in these patients, the threshold to proceed to vitreous biopsy and empirical intra-vitreous antibiotics should be low.

29. Conclusion

Patients suspected of having endophthalmitis following ocular surgery or trauma require prompt evaluation and treatment. Patients having ocular symptoms and signs in the absence of trauma or ocular surgery and presence of risk factors such as diabetes, cardiac disease, renal disease, organ transplantation, immunodeficiency status and malignancy should be evaluated for endogenous endophthalmitis. Since endophthalmitis can be caused by a large number of bacterial as well as fungal species, it requires rapid identification of the causative organism. Visual prognosis depends mainly on the underlying microorganisms, and it is particularly poor in cases of infection with Gram-positive bacteria or Aspergillus species. Experience has shown that early Vitrous biopsy along with intra-vitreal antibiotics may save vision in some patients while in other patients pars-plana vitrectomy may be necessary to prevent total loss of vision and perhaps an eye.

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