MANAGEMENT OF ENDOPHTHALMITIS

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Abstract: *Endophthalmitis is the most feared and devastating complication of intraocular procedures and can lead to a permanent, complete loss of vision. Endophthalmitis is defined as an inflammation of internal layers of the eye, resulting from intraocular colonization of infectious agents and manifesting with an exudation into the vitreous cavity. Worldwide, the reported incidence of post-operative endophthalmitis is 0.04- 4%. Post cataract surgery incidence is 0.265% (more with clear corneal incision), post keratoplasty 0.382% and post vitrectomy 0.05%. The incidence of bleb associated infection is 0.2% to 9.6% and post intravitreal injection is around 0.038% and varies from 0.021% to 0.045%. A series of endophthalmitis cases may force a temporary shutdown of the operation theatre.*

Infectious endophthalmitis is a potentially devastating condition involving the internal structures of the eye. It is one of the most feared complications of cataract extraction and other intraocular surgeries. Rarely, it can occur endogenously from a systemic nidus of infection.

Endophthalmitis is classified on the basis of the source of the infection, as exogenous, which is the most common subtype, or endogenous. The avascular densely packed collagenous matrix of the cornea and sclera serves as a potent barrier against infectious infiltration in normal eyes.

Violation of these structures, typically by surgery or trauma, makes eye susceptible to entry of pathogenic organisms, and may lead to exogenous endophthalmitis. Bacteria are often causative agents in these cases. There are typically no associated systemic findings such as fever and minimal, if any, peripheral leukocytosis.

Endogenous endophthalmitis occurs in otherwise healthy eyes in association with transient or persistent bacteremia or fungemia. It is observed most frequently in immunosuppressed patients and intravenous drug users, and less commonly in patients with cardiac valvular disease, persistent sites of infection elsewhere in the body, and in those undergoing dental work. Fungal infections are most common, but a third of patients will present with bacterial endophthalmitis, often caused by gram-negative species.

CLASSIFICATION OF ENDOPHTHALMITIS

Infectious endophthalmitis is classified by the events leading to the infection and by the timing of the clinical diagnosis. The broad categories include postoperative endophthalmitis (acute-onset, chronic or delayed-onset, conjunctival filtering-bleb associated), post traumatic endophthalmitis, and endogenous endophthalmitis. Miscellaneous categories include cases associated with microbial keratitis, intravitreal injections. These categories are important in predicting the most frequent causative organisms and in guiding therapeutic decisions before microbiologic confirmation of the clinical diagnosis.

Endophthalmitis classification and Most Frequently Reported Organisms are

CATARACT SURGERY

Post-cataract endophthalmitis[1,2] is categorized on the basis of the time to onset following surgery, as acute (within 6 weeks) or delayed (Table 1). The incidence of endophthalmitis after cataract extraction is reported to be 0.04–0.265%. Some authors suggest an increase in the incidence of endophthalmitis beginning in the late 1990s/2000, in parallel with the increased use of clear cornea cataract wound placement. Post-cataract

Table 1: Classification of Endophthalmitis

CATEGORY	ORGANISMS RESPONSIBLE
1. Postoperative endophthalmitis	
(a) Following cataract surgery: Acute-onset postoperative endophthalmitis Starts within 6 weeks	Coagulase (−) Staphylococci, Staphylococcus aureus, Streptococcus, gram-negative bacteria
(b) Following cataract surgery: Delayed-onset postoperative endophthalmitis	P. acnes, coagulase (−) Staphylococci, fungi
(c) Following glaucoma surgery: Conjunctival filtering bleb-associated endophthalmitis	Streptococcus species, Haemophilus influenzae, Staphylococcus species
(d) Following glaucoma surgery: Endophthalmitis associated with glaucoma drainage devices	
(e) Following elective corneal transplant	
2. Posttraumatic endophthalmitis	Bacillus species (30–40%), Staphylococcus species
3. Endogenous endophthalmitis	Candida species, Staphylococcus aureus, gram-negative bacteria
4. Endophthalmitis associated with keratitis	Pseudomonas, Staphylococcus species
5. Endophthalmitis associated with intravitreal injection	Gram positive 91 % (Coagulase negative staph 78 %)

Table 2: TASS Versus Postoperative Endophthalmitis		
	Toxic anterior segment syndrome	**Endophthalmitis**
Cause	Noninfectious reaction to toxic agent present in BSS solution Antibiotic injection Endotoxin Residue	Bacterial, fungal, or viral infection
Onset	12-24 h	3-7 days
Signs/symptoms	Blurry vision Pain: None, or mild-to-moderate Corneal edema: Diffuse, limbus to limbus Pupil: Dilated, irregular, nonreactive Increased IOP Anterior chamber: Mild-to-severe reaction with cells, flare, hypopyon, fibrin Signs and symptoms are limited to anterior chamber Gram stain and culture negative Ultrasound is anechoic	Decreased VA Pain (25% have no pain) Lid swelling with edema Conjunctival injection Hyperemia Anterior chamber: Marked inflammatory response with hypopyon Vitreous involvement Inflammation in entire Ocular cavity. Ultrasound shows vitreous echoes
Treatment	Intensive corticosteroids No intravitreal injection Monitor IOP closely Watch closely over next few hours for signs of bacterial infection	Culture anterior chamber and vitreous Intravitreal and topical antibiotics Vitrectomy

endophthalmitis is typically associated with defects in surgical wound and violation of lens capsule, which can provide a route of entry for infectious agents. The patient's own periocular flora is source of infection in majority of cases of endophthalmitis. In 68–82% of post-cataract endophthalmitis cases, an identical genetic or molecular signature was present in vitreous isolates and commensal bacteria occupying the patient's conjunctiva, eyelids or nose. Gram positive organisms account for 90% or more of pathogens isolated in culture positive cases of postoperative endophthalmitis following cataract surgery, with coagulase-negative Staphylococci (Staphylococcus epidermidis) and Staphylococcus aureus representing the leading causes. However, in India, Gram negative organisms and fungi are important in etiology. 5% povidone iodine solution is able to reduce incidence of endophthalmitis.

In delayed onset endophthalmitis, Propionibacterium acnes is the most commonly implicated pathogen, accounting for nearly 40% of isolates. It has a subtle presentation and indolent course.

Patient symptoms indicative of endophthalmitis include ocular pain, diminished vision and headache. Although pain is an important symptom, it is not universal. It is important to differentiate infective endophthalmitis from sterile post-op inflammation. Toxic Anterior Segment Syndrome (TASS) is an acute post-operative inflammatory reaction in which a noninfectious substance enters the anterior segment and induces toxic damage to the intraocular tissues. Almost all cases occur after uneventful cataract surgery (Table 2).

GLAUCOMA FILTRATION PROCEDURES

Glaucoma surgery is associated with endophthalmitis in 0.2 to 9.6% of cases. Endophthalmitis following glaucoma surgery, unlike post cataract infections, tends to be delayed and is often associated with prior episodes of blebitis. Diabetes, use of anti-metabolites as well as inferior bleb location increases risk and hastens onset of endophthalmitis. Delayed onset bleb-related endophthalmitis is associated with Streptococcus species (25%) and gram-negative organisms, particularly Haemophilus influenzae (18%).

INTRAVITREAL INJECTIONS

Intravitreal injections of triamcinolone have a 0.87% incidence of infectious endophthalmitis, possibly due to inhibition of immune function. Intravitreal ANTI VEGF drug injection is associated with endophthalmitis rate of 0.038% and varies from 0.021% to 0.045% .Diabetics may be at higher risk, however. The majority of the cases are caused by Streptococcus or Staph species representing commensal flora of ocular adnexa and oropharynx. The risk of infection may be lessened by decreasing oropharyngeal droplet transmission at time of the injection.

The use of compounding pharmacies, which involves the alliquoting of a single medication such as Avastin into multiple intravitreal injections, may increase incidence of infection and has been associated with local outbreaks of endophthalmitis. Avastin vial may be adulterated also and cold chain may have broken and hence contain toxins. So even if the vial is opened on the table and patient given intravitreal injection patient will develop symptoms like TASS. In case of avastin symptoms will be localized in posterior segment so this should be called Toxin Posterior Segment Syndrome and not Toxin Anterior Segment Syndrome. These symptoms will develop in few hours and are a type of sterile reaction to toxins. However, if the avastin gets infected during compounding then infective endophthalmitis will develop. It is extremely severe due to direct inoculation of organism in vitreous. Prognosis is very poor, and vitrectomy is frequently required. Lucentis scores over Avastin because of its efficacy and safety. Safety with regard to the preparation of Avastin is always a source of concern as there is no uniform method; multiple pricks are involved during alliquoting. There have been incidents of cluster endophthalmitis with Avastin.

TRAUMA

The risk of endophthalmitis following open globe injuries ranges from 4.2 to 7%. In contrast, following closed globe injuries, endophthalmitis is exceedingly rare. Staphylococcal species are most common causative agents in trauma-related endophthalmitis, and some species such as Bacillus cereus are seen only in trauma. The source of the infection is typically the penetrating material. The rate of infection rises dramatically to 10–15% when an IOFB is present and if the repair is delayed beyond 24 hours of the injury. Even without overt infection, prophylactic intravitreal antibiotics should be considered at the

time of the IOFB removal, since in nearly a quarter of patients cultures of the IOFB will be positive for bacteria, and risk of intravitreal antibiotics is generally low. In rural settings, where organic material contamination is common, endophthalmitis following penetrating ocular trauma achieves rates as high as 30%, with Bacillus species isolated in 46% of cases and polymicrobial isolates in 42%.

TASS (TOXIC ANTERIOR SEGMENT SYNDROME)

In TASS, most develop symptoms within 12-24 hrs, there is decrease in visual acuity, corneal edema is from limbus to limbus, there is moderate to severe AC reaction with cells, flare, hypopyon and fibrin, pupil may be dilated and non-reactive and IOP may be normal or raised.

Post operative endophthalmitis usually presents after 72 hours (3 days). Most common causative agents are gram positive coagulase negative organisms. However in India, gram negative organisms and fungi are also important. Differentiation of TASS and post operative endophthalmitis is important as management and prognosis of TASS is significantly different. Delay in diagnosis leads to delay in initiating appropriate treatment.

ANTIMICROBIAL THERAPY

The target area for microbial therapy in endophthalmitis is vitreous cavity (Table 3). Intravitreal therapy is the cornerstone of antimicrobial administration. Because most cases of endophthalmitis manifest as acute fulminant infections, the initial antibiotic administration is usually made without culture results to identify the organism definitively. The choice of agent administered initially is therefore empirical. Broad-spectrum coverage is important, and choice depends in part on microbes expected in a given clinical setting.

PARS PLANA VITRECTOMY

PPV plays a role in many phases of endophthalmitis therapy (Table 4). As initial therapy it is validated by the EVS[3,4] results only for acute post cataract extraction infections in eyes presenting with vision of hand motions or less. In addition to use as initial therapy in many of these clinical settings, PPV should also be considered for eyes not responding

Table 3: Preparation of intravitreal antibiotics

ANTIBIOTIC	Vial contains	Intravitreal dose	PREPARATION
VANCOMYCIN Diluent used is water for injection or ringer lactate	500mg powder	1mg in .1 ml	Add 10 ml. 500 mg in 10 ml. 50 mg in 1 ml. 10 mg in .2 ml. take .2 ml. make it 1.0 ml. 1 ml contain 10 mg. .1 ml contains 1 mg.
CEFTAZIDIME	500 mg powder	2.25 mg in .1 ml	Add 2 ml. 500 mg in 2 ml. 250 mg in 1 ml. 22.5 mg in .1 ml. Take .1 ml. make it 1.0 ml. 1 ml contains 22.5 mg. .1 ml contains 2.25 mg
DEXAMETHASONE	8 mg / 2 ml 4mg / 1ml .4 mg / .1 ml	.4mg in .1 ml	Take .1ml directly It contains .4 mg
AMIKACIN	100 mg in 2ml 50 mg in 1 ml 10 mg in .2 ml	400 µ gm (.4 mg) in .1 ml	Take .2 ml containing 10 mg. Add 2.3 ml. make it 2.5 ml. 2.5 ml contains 10 mg .1 ml contains 400 µ gm
GENTAMCIN	80 mg in 2ml 40 mg in 1ml 4mg in .1 ml	200 µgm (.2 mg) in .1 ml	Take .1 ml containing 4 mg. Add 1.9 ml. make it 2 ml. 4 mg in 2 ml. 2mg in 1ml. .2 mg in .1 ml.

Table 4: Decision-making tree to select the treatment in endophthalmitis

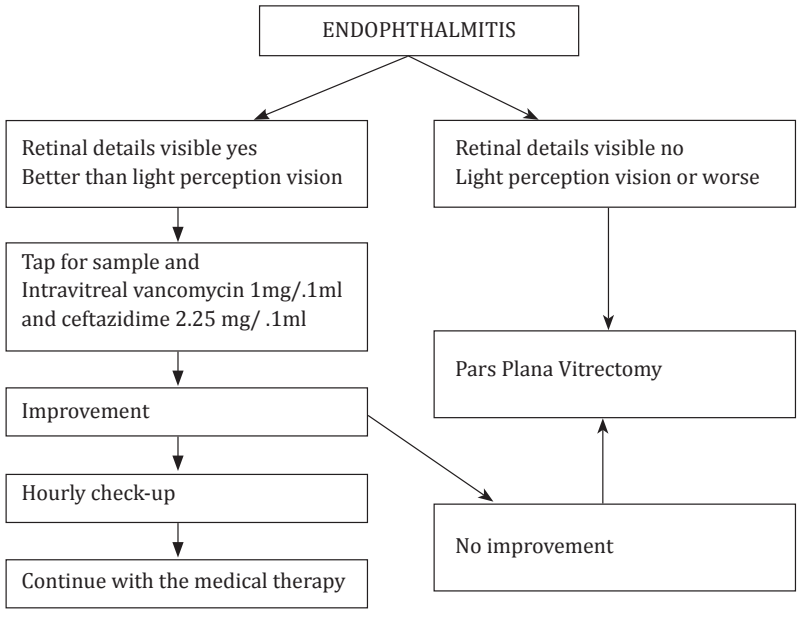


Table 5: Authors Recommended Regimen[5,6]	
Treatment	**Authors' recommended regimen**
Intravitreal antibiotics	Vancomycin 1 mg/0.1 ml and Ceftazidime 2.25 mg/0.1 ml
Intravitreal steroids	Dexamethasone 0.4 mg/0.1 ml (optional)
Subconjunctival antibiotics	Vancomycin 25 mg and Ceftazidime 100 mg (optional)
Topical antibiotics	Vancomycin 25 mg/ml and Ceftazidime 50 mg/ml or Moxifloxacilin topical antibiotics
Topical cycloplegics	Cyclopentolate or atropine drops

to an original tap-and-inject strategy, and may be necessary to clear vitreous opacities in eyes cured of infection when spontaneous clearing does not occur.

PREOPERATIVE EVALUATION

A careful and extensive history should be taken. Clinical details such as systemic infectious disease, type of eye injury, or previous surgery may hold important clues to the identity of the infecting organism. Particular attention should be paid to the length of time from the surgical insult or trauma to the onset of symptoms and to the time that has passed since symptoms began. Previous antibiotic or corticosteroid therapy should be noted. A thorough ocular examination should include a careful search for any possible route of entry for the infecting organism. The effects of the inflammation should also be noted: corneal clarity and thickness, condition of any surgical wound, degree of anterior-chamber reaction, hypopyon, clarity of the vitreous, visibility of the retina, and presence or absence of a red reflex. USG can define the degree of condensation of the vitreous, determine whether the retina is attached, and identify choroidal swelling.

MANAGEMENT

At present, best choice of intravitreal antibiotics is Vancomycin (1 mg in 0.1 ml) combined with Ceftazidime (2.25 mg in 0.1 ml) in separate syringes (Table 5).

Alternatively, Vancomycin may be combined with Amikacin (400 µg in 0.1 ml).

Intravitreal antibiotics are the key to management because levels above the minimum inhibitory concentration of most pathogens are achieved, and are maintained for days. They should be administered immediately after culture specimens have been obtained. Antibiotics commonly used in combination are ceftazidime, which will kill most Gram-negative organisms (including Pseudomonas aeruginosa) and vancomycin to address Gram-positive cocci (including methicillin-resistant Staphylococcus aureus). The antibiotics are injected slowly into the mid-vitreous cavity. After the first injection has been given, the syringe may be disconnected but the needle left inside the vitreous cavity so that the second injection can be given through the same needle; alternatively a second needle can be used.

Intravitreal vancomycin provides broad coverage for gram-positive organisms and ceftazadime is effective against gram-negative bacteria observed in post-operative endophthalmitis .

SURGICAL INTERVENTION

The results of EVS study are still applicable to post-cataract endophthalmitis cases today, with some modifications. In post-cataract patients presenting with intraocular inflammation and a visual acuity at the level of light perception, PPV with injection of intravitreal antibiotics appeared to improve the visual outcomes compared with intravitreal antibiotics alone. For patients with visual acuity of hand motion or better, PPV with intravitreal antibiotics appeared to provide no additional visual benefit compared with intravitreal antibiotics alone.

SURGICAL INTERVENTION

The main goals of PPV in endophthalmitis are to obtain sufficient tissue for diagnosis and to debulk the pro-inflammatory debris. In practice, a culture result of the removed material alters clinical management in less than 5% of cases. While the EVS included limited vitrectomy, more extensive debridement may provide better outcomes. Removal of the IOL is typically not required, except in cases of chronic low-grade endophthalmitis associated with P. acnes resistant to medical therapy.

WHEN TO DO PPV

After intravitreal antibiotics, patient is monitored for 24-36 hours. If there is worsening, patient has to be taken up for surgical intervention in the form of PPV. If there is no worsening, medical treatment can be continued for 48 hours following which decision regarding additional intravitreal antibiotics or surgical intervention is to be taken. Improvement in fundus glow with decrease in hypopyon is indicative of clinical improvement. Medical treatment should be continued.

In situations where there is a partial response to intravitreal antibiotics with resolution of hypopyon but persisting AC reaction (3-4+), further intravitreal antibiotics are not preferred, conservative medical management is continued and patient is readied for surgical intervention.

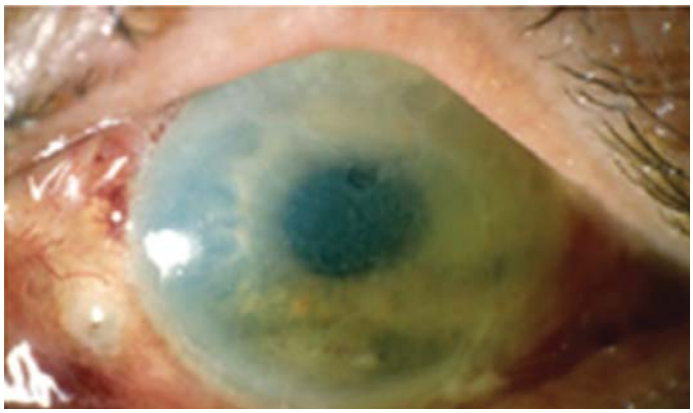
In situations where there is no response to intravitreal antibiotics or in very severe infection, RADICAL pars plana vitrectomy with peeling of hyaloid and base dissection is required. There is no role for core vitrectomy in this situation.

IOL removal during vitrectomy for endophthalmitis may be indicated in severe endophthalmitis, P acne endophthalmitis, fungal endophthalmitis and recurrent endophthalmitis.

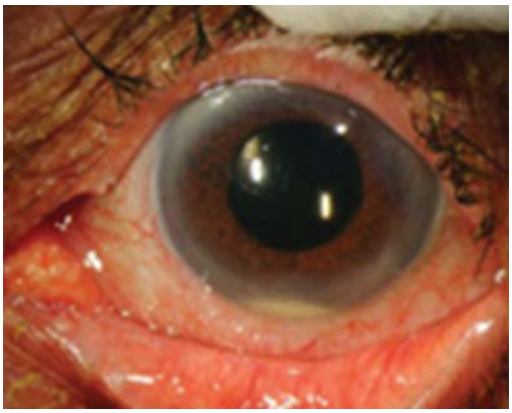
CONCLUSION

Endophthalmitis remains a devastating complication of intraocular surgery and penetrating ocular trauma despite recent advances in diagnosis and treatment. Two-thirds of cases are postoperative, and 20–25% occur after penetrating trauma. Gram-positive organisms predominate in incidence and usually fare better than Gram-negative infections, with Staph epidermidis having a better prognosis than S. aureus. Fungal endophthalmitis accounts for 5–10% of all cases. Intravitreal antibiotics are well established as the mainstay of treatment for endophthalmitis because of the poor penetration of antibiotics into the vitreous cavity when administered by other routes because of the blood–retina barrier.

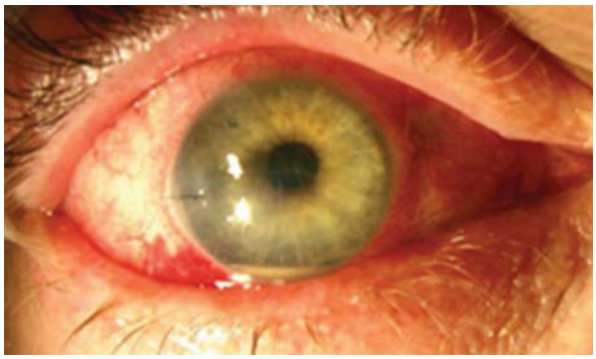
Pars plana vitrectomy has the advantage of removing bacteria and their toxins and clearing the ocular media, allowing a more rapid visual recovery. The eye is sterilized more quickly and reliably. Most authors recommend vitrectomy as the initial therapy for



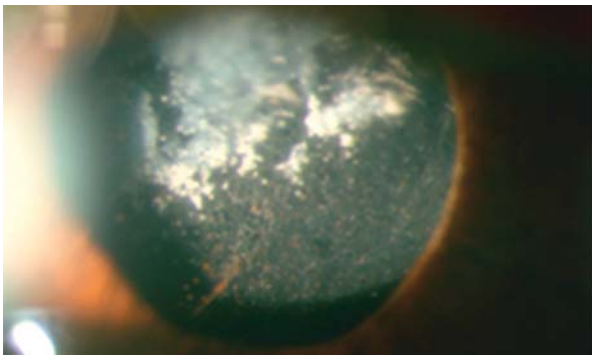
1st case: *On postoperative day 1, there is significant AC reaction with hypopyon and good fundal glow. There may be a dilemma of whether to initiate intravitreal antibiotics or intensive topical and systemic steroids. In view of BCVA better than 6/60 and because it started within 24 hours of surgery, this may be treated as Toxic Anterior Segment Syndrome with topical and IV steroids but requires close follow-up. Dilate the pupil with cyclopentolate, atropine and tropicamide in front of you (Figure 1).*



2nd case: *A 60-year-old male presented 4 days after cataract surgery with acute-onset endophthalmitis (Staphylococcus epidermidis). Clinical presentation included sudden onset decrease in visual acuity, conjunctival hyperemia, corneal edema, and hypopyon. Treatment is intravitreal vancomycin 1mg / . 1 ml and ceftazidime 2.25 mg / .1 ml to which patient responded and improved (Figure 2).*

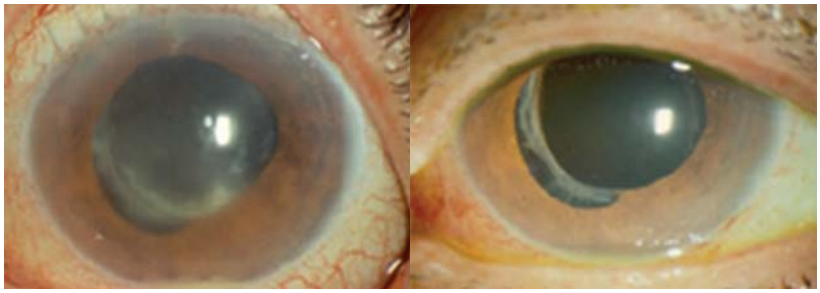


3rd case: *A 69-year old male with acute-onset endophthalmitis (coagulase-negative staphylococci) presented 3 days after cataract surgery. A suture was placed in temporal clear corneal incision during surgery to ensure wound stability after the cataract surgery. However despite that, endophthalmitis occurred. Treatment is intravitreal vancomycin 1mg / .1ml and ceftazidime 2.25 mg / .1ml. (Figure 3).*



4th case: *A 72-year-old woman 3 months status post uncomplicated cataract surgery in the left eye complains of blurry vision for 2 weeks. The cornea is clear, there is a mild anterior chamber reaction, and the IOL is centered in the bag. The culture is positive for P. acnes. P. acnes endophthalmitis is treated with intraocular vancomycin and topical steroids. It usually also requires a vitrectomy, injection of vancomycin into the capsular bag, partial or total capsulectomy, and IOL removal or exchange (Figure 4).*

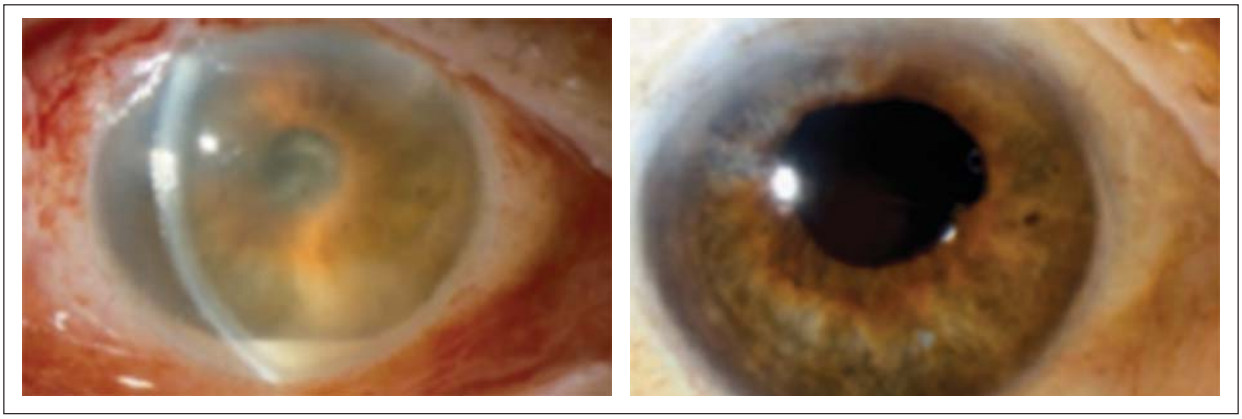
fungal infections, for Propionibacterium acnes infections and for traumatic endophthalmitis. In bacterial infections, immediate vitrectomy is recommended for the most severe infections, including clinical settings such as filtering blebs, which are known to have a high incidence of virulent organisms. Vitrectomy is then followed by intraocular antibiotic injection. Infections after trauma have a poorer prognosis than postoperative cases after cataract extraction. The length of time from onset of infection to initiation of therapy and differences in virulence from one strain of bacteria to another are other important factors in outcome.



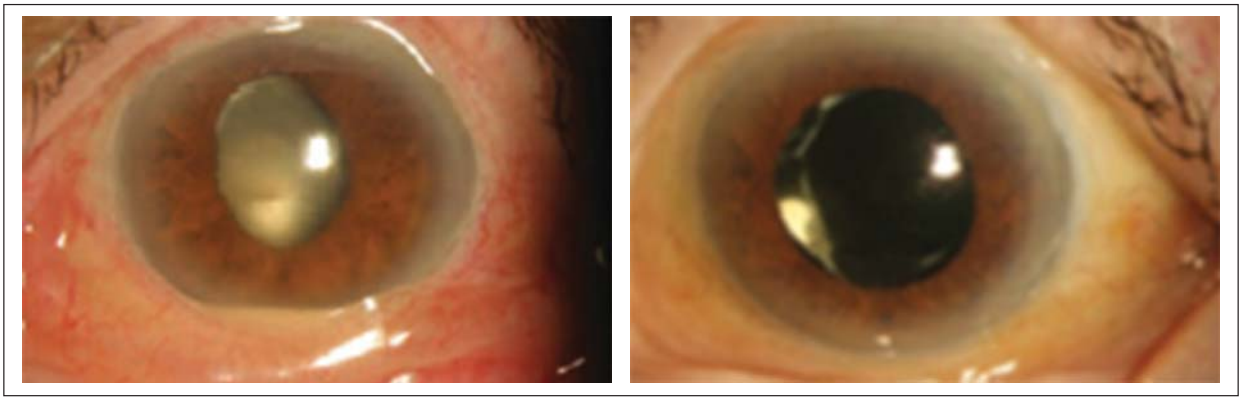
5th case: *A 79-year-old female patient with delayed-onset postoperative endophthalmitis following cataract surgery presented with gradual painless decrease in vision, conjunctival congestion, mild corneal edema, capsular plaque, and hand motions (HM) vision. Patient underwent pars plana vitrectomy and intraocular antibiotics injection in the capsular bag behind the intraocular lens. The vitreous culture was positive for Propionibacterium acnes (Figure 5a).*
At 6-month follow-up, the patient regained best corrected visual acuity of 20/30 with resolution of inflammation (Figure 5b).

SOME INTERESTING CASES[7,8]

Treatment of endophthalmitis spans from dilators, cycloplegics and steroids for TASS to intravitreal antibiotics for mild to moderate endophthalmitis, to PPV for very severe and fulminant cases. So one should first make distinction between toxic reaction and infection and then select the appropriate modality of treatment.



6th case: *Acute-onset endophthalmitis. A 78-year-old male patient with acute-onset postoperative endophthalmitis 2 day following cataract surgery. The patient presented with conjunctival congestion, moderate corneal edema, hypopyon, fibrinous membrane in anterior chamber, hazy view of the posterior segment, and light perception (LP) vision. The patient underwent pars plana vitrectomy and intravitreal vancomycin and ceftazidime. The vitreous culture was positive for Serratia marcescens (Figure 6a). At 1-year follow-up, the patient regained best corrected visual acuity of 20/50 (Figure 6b).*



7th case: *Endophthalmitis after intravitreal injection. A 56-yearold male patient presented 1 day after intravitreal anti-VEGF injection for age-related macular degeneration (AMD) with sudden painful decrease in vision. The patient presented with conjunctival congestion, conjunctival chemosis, hypopyon, fibrinous membrane in the anterior chamber, hazy view of the posterior segment, and hand motions (HM) vision. The patient underwent vitreous tap and intraocular injection (vancomycin, ceftazidime). The vitreous culture was positive for coagulase-negative Staphylococcus (Figure 7a). At 1-year follow-up, the inflammation and infection resolved with best corrected visual acuity improved to 20/50 (Figure 7b).*

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