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Update of the management of postoperative endophthalmitis

術後眼內炎治療的最新發展

Postoperative endophthalmitis is a rare but potentially devastating complication of intra-ocular surgery. Most cases are caused by bacterial infection. The clinical presentation of endophthalmitis can be classified as acute postoperative endophthalmitis, chronic postoperative endophthalmitis, and bleb-associated endophthalmitis. They each have a different aetiology, treatment, and prognosis. This review discusses these features, as well as the microbiology, diagnosis, and treatment outcomes of these three types of inflammation, with particular emphasis on recent advances in their management. The role of steroids, systemic fluoroquinolones, and the choice of antibiotic against gram-negative bacteria are still controversial and need further study. Moreover, the management of chronic postoperative and bleb-associated endophthalmitis has not been standardised, and no conclusive findings on the efficacy of the various prophylactic measures are available. Thus, the treatment and prevention of postoperative endophthalmitis remain a clinical challenge.

術後眼內炎是眼科手術後一種罕見但破壞力極強的併發症，通常由細菌感染引起。眼內炎按臨床病徵可分為急性術後眼內炎、慢性術後眼內炎，以及胸膜下肺大疱相關眼內炎，各自的病因、療法和預後都有所不同。本文闡釋了這三方面的特點，並就這三種炎症的微生物學特點、診斷及治療結果加以討論，當中特別說明了治療方法的最新發展。類固醇、系統性氟喹諾酮類的作用，以及採用抗生素對付革蘭氏陰性桿菌，仍具爭論性，需要進一步研究。此外，慢性術後眼內炎、胸膜下肺大疱相關眼內炎的療法還沒有標準，各種預防措施的功效也沒有定論。因此，治療和預防術後眼內炎對醫護人員來說仍然是一個挑戰。

Key words:
Antibacterial agents;
Blister;
Endophthalmitis;
Postoperative complications;
Vitrectomy

關鍵詞：
抗菌劑；
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Introduction

Endophthalmitis is inflammation in the ocular cavity and the surrounding tissues, but not extending to the sclera. Most cases are caused by bacterial infections after eye surgery—especially after cataract or glaucoma surgery. The incidence of postoperative endophthalmitis has decreased during the past century.[1] It has decreased from approximately 10% in the late 1800s to 0.58% in the mid-1900s to 0.09% in the mid-1990s. Advances in microsurgical and aseptic techniques and prophylactic broad-spectrum antibiotics, in combination with a better understanding of the pathophysiology of infection, may explain this trend.[1] In a recent 7-year retrospective review of acute postoperative endophthalmitis, the overall infection rate was 0.05%.[1] The incidence depended on the type of procedure: it was highest for glaucoma surgery (0.20%), followed by penetrating keratoplasty (0.08%), cataract extraction (0.04%), pars plana vitrectomy (0.03%), and secondary intra-ocular lens placement (0.20%).

Source of infection and risk factors

Potential sources of infection include contaminated instruments or irrigation solutions, but the most common source is the patient's own ocular flora.[2] Microorganisms from the conjunctival sac can enter the eye during or after surgery through a wound. There are many risk factors underlying postoperative endophthalmitis. Preoperative risk factors include blepharitis, lachrymal duct obstruction, the wearing of contact lenses, the existence of an ocular prosthesis in the other eye, and secondary intra-ocular lens implantation. Intra-operative risk factors include inadequate eyelid or conjunctival disinfection, surgery lasting more than 60 minutes, loss of vitreous humour, use of a prolene haptic intra-ocular lens, and unapparent or unplanned ocular penetration. Postoperative risk factors include wound abnormalities, inadequately buried sutures, suture removal, vitreous incarceration in the surgical wound, and the presence of a filtering bleb. Furthermore, clear corneal incisions during cataract surgery impart a higher risk of infection than scleral tunnel incisions,[3] perhaps because a stable, selfsealing incision is more difficult to construct in the cornea than in the sclera. The incision site of clear corneal incisions in the temporal region may also play a role.

Classification

The clinical presentation of endophthalmitis can be classified into the following three categories: acute postoperative endophthalmitis, chronic postoperative endophthalmitis, and bleb-associated endophthalmitis. They each have a different aetiology, treatment, and prognosis.

Acute endophthalmitis occurs within 6 weeks of surgery, most commonly cataract surgery. The Endophthalmitis Vitrectomy Study (EVS)[4] found that 70% of cultures grew coagulase-negative *Micrococcus* (mostly *Staphylococcus epidermidis*); 10% grew *Staphylococcus aureus*, 9% *Streptococcus* species, 2% *Enterococcus* species, 3% other gram-positive bacteria, and 6% gram-negative bacteria.

Chronic endophthalmitis occurs more than 6 weeks after surgery. The most common organisms causing infection include *Propionibacterium* species (eg *P acnes*), fungi (primarily *Candida* species, eg *C parapsilosis*), and *S epidermidis*. Less commonly, anaerobic *Streptococcus* species, *Actinomyces* species, *Nocardia asteroides*, *Alcaligenes xylosoxidans*, and *Corynebacterium* species can also be cultured.

Endophthalmitis may occur weeks to years after glaucoma filtration surgery. There are two types of infection: blebitis (a presumed bleb infection without vitreous involvement) and bleb-associated endophthalmitis (one with vitreous involvement, which usually develops months or years after surgery, and, rarely, may occur in the early postoperative period).Blebitis and bleb-associated endophthalmitis, however, may represent a spectrum of disease.[5] Early-onset bleb-associated endophthalmitis is usually caused by less virulent organisms than those in the other forms of endophthalmitis, such as *S epidermidis* and *P acnes*.[5] Delayed-onset endophthalmitis is usually caused by more virulent *Streptococcus* species (41%) and gram-negative bacteria (31%)—for example, *Haemophilus influenzae*.[6]

Box 1. Summary of techniques used when performing aqueous and vitreous taps and intravitreal injection[8]

General requirements
(1) Aseptic treatment room
(2) Patient preferably supine, but could be at a slit lamp
(3) Topical and retrobulbar or peribulbar anaesthesia
(4) Eyelid skin sterilised with povidone-iodine 5% solution
(5) Two drops or a swab soaked with povidone-iodine applied to conjunctival sac at the temporal aspect of the limbus, followed by a washout with balanced salt solution
(6) Eyelid speculum
(7) Globe fixation with toothed forceps 180° away from site of paracentesis

Aqueous tap
(1) Perform anterior-chamber paracentesis at the limbus with a 30-Gauge (G) needle attached to a tuberculin syringe
(2) Aspirate 0.1-0.2 mL; avoid endothelium or lens contact
(3) Inject air 0.1 mL into the anterior chamber if totally collapsed

Vitreous tap and antibiotic injection
(1) Use myringo-vitreo-retinal blade to enter through the conjunctiva and sclera 4.0 mm from the limbus if phakic, or 3.5 mm from the limbus if aphakic
(2) Aspirate 0.2 mL of the vitreous humour with a 23-G needle on a tuberculin syringe; needle pointing to the mid-vitreal cavity
(3) Intravitreal antibiotic injection at the same entry site using a 27-G needle with the bevel facing up; inject slowly into anterior vitreal cavity

Microbiology
Available aqueous and vitreous specimens are immediately processed:
(1) Inoculate blood and chocolate agar plates, Sabouraud' s medium, thioglycolate medium before use
(2) Apply to glass slide for gram and Giemsa staining

Diagnosis

Acute postoperative endophthalmitis is a serious complication and requires prompt recognition and immediate attention, because it can result in severe loss of vision. Patients may exhibit symptoms of pain, photophobia, floaters, and reduced vision. Examination may reveal lid swelling, conjunctival chemosis, corneal stromal oedema, keratic precipitates, an inflamed anterior segment (eg a variable hypopyon), and vitritis.[7] However, retinal detachment, inflammatory reaction to contaminants on the intra-ocular lens, anterior segment ischaemia, and pre-existing uveitis may all be confused with postoperative endophthalmitis.[2]

Accurate diagnosis of postoperative endophthalmitis can be confirmed by staining and culturing the pathogenic organisms present in the eye. Diagnosis by polymerase chain reaction analysis is a recent advancement; the method has a higher sensitivity and shorter detection time than conventional staining and culture.[7] In the case of acute postoperative endophthalmitis, both aqueous and vitreous humours should be tested. For chronic postoperative endophthalmitis, all intra-ocular plaques should be cultured and stained. Bleb-associated endophthalmitis can be identified by microbiological culture of contact lenses; aqueous and vitreous humours; and possibly the bleb contents. Box 1 shows a summary of the techniques for aqueous and vitreous puncture tests (taps) and intravitreal injection.[8]

Treatment of acute postoperative endophthalmitis

The EVS[4] was a multicentred, randomised controlled clinical trial that was designed to compare the roles of immediate pars plana vitrectomy and immediate tap or biopsy. The role of systemic antibiotics in the management of acute endophthalmitis after cataract surgery was also assessed. The EVS started in 1991, involved 24 centres in the United States, and initially enrolled 420 patients. Patients were eligible for inclusion in the EVS if they showed clinical signs and symptoms of bacterial endophthalmitis in an eye that had undergone cataract surgery or lens implantation within 6 weeks of the onset of infection. The eyes had to have a visual acuity ranging from 20/50 or worse and be perceptive to light.

Intra-ocular antibiotic therapy

For decades, intravitreal antibiotic therapy has been the principal course of treatment for acute postoperative endophthalmitis. This route results in a far greater intra-ocular antibiotic concentration than any other method of administration. Because of the importance of prompt treatment and the inaccuracies of gram-staining results, broad-spectrum intravitreal antibiotics that are effective against both gram-positive and gram-negative bacteria are administered even before the culture results are available.

Vancomycin is considered the drug of choice for the range of infections encountered with acute postoperative endophthalmitis; antibiotic coverage of *Staphylococci* species is critical. Vancomycin is non-toxic and the EVS[5] recommended a dose of 1.0 mg in 0.1 mL. All gram-positive organisms, including methicillin-resistant *Staphylococcus aureus*, were shown to be susceptible to the antibiotic.[5] The choice of antibiotics used to treat gram-negative organisms, however, remains controversial. Aminoglycosides, such as amikacin or gentamicin, are often used, and ceftazidime—a third-generation cephalosporin—is a recent alternative. Although intravitreal use of vancomycin is generally safe, intravitreal use of aminoglycosides, especially gentamcin, has been reported to cause macular toxicity.[9] Aminoglycoside-induced macular infarction is thought to result from an increase in the aminoglycoside concentration, which is caused by the gravity-induced accumulation of drugs on the macula in a supine patient. Another factor may be the higher density of ganglion cells in the paramacular area than in the other areas of retina. The primary toxicity of aminoglycosides is to the neurons and glia of the inner retina, with resultant inflammation and leukocyte plugging of retinal capillaries, leading to ischaemia and infarction. Although animal experiments[10] have shown that amikacin is safer than gentamicin, its potential for macular toxicity still exists. Ceftazidime, in contrast, carries a lower risk of retinal toxicity and has a broader therapeutic index than these two drugs. Kwok et al,[11] however, have shown that in-vitro ceftazidime precipitates in vitreous humour at body temperature, irrespective of the presence of vancomycin.

Table 1. Advantages of administering intravitreal amikacin or ceftazidime[12]

Amikacin	Ceftazidime
Concentration-dependent killing	Lower risk of retinal toxicity
Less susceptible to ‘ inoculum effects’	Broad therapeutic index
Synergy with vancomycin against *Enterococci*, other *Streptococci*, and *Staphylococci* species	More effective in the vitreous humour for endophthalmitis
Broader spectrum antibiotic	
No precipitation	

A comparison of the advantages of using either amikacin or ceftazidime are summarised in Table 1.[12] In cases in which vancomycin-resistant *Enterococci* species are suspected, ampicillin—an aminoglycoside—and systemic ciprofloxacin should be considered empirical therapy.[13] Repeated vitreous tapping and injection of antibiotics, together with pars plana vitrectomy (if not originally performed), should be considered if there is no clinical improvement or if the condition deteriorates within 48 to 72 hours.[14] However, prolonged use of aminoglycosides should be avoided because of retinal toxicity[15]: a relatively small increase in concentration can cause considerable toxicity; accordingly, careful preparation and accurate dosage are of utmost importance.

Systemic antibiotic therapy

The EVS showed that the additional use of intravenous ceftazidime and amikacin did not improve the final acuity or media clarity when compared with the use of systemic antibiotics. Furthermore, intravenous administration of vancomycin yielded an inadequate antibacterial effect because it could not reach therapeutic levels in the aqueous and vitreous humours.[16,17]

Older-generation fluoroquinolones, such as ciprofloxacin and ofloxacin, are increasingly ineffective against some of the pathogens most commonly responsible for postoperative endophthalmitis; however, the newer-generation antibiotics show promising results. Mather et al[18] described the fourth-generation fluoroquinolones, for example, gatifloxacin, as “new weapons in the arsenal of ophthalmic antibiotics”. These drugs not only display an activity against gram-negative bacteria equivalent to that of older-generation fluoroquinolones, but also demonstrate enhanced potencies against gram-positive bacteria. In addition, Hariprasad et al[19] reported that orally administered gatifloxacin was able to penetrate into the non-inflamed human eye, to reach therapeutic levels in the aqueous and

Table 2. Recommended doses for treatments of infective postoperative endophthalmitis

Route of administration	Drug	Dose
Intravitreal	Vancomycin	1.0 mg in 0.1 mL[24]
	Ceftazidime	2.25 mg in 0.1 mL[13]
	Amikacin	0.4 mg in 0.1 mL[24]
	Dexamethasone	0.4 mg in 0.1mL[25]
Subconjunctival	Vancomycin	25 mg in 0.5 mL[24]
	Ceftazidime	100 mg in 0.5 mL[24]
	Dexamethasone	4-8 mg[24]
Topical	Vancomycin	50 mg/mL drops every hour[24]
	Amikacin	20 mg/mL drops every hour[24]
	Prednisolone acetate (1%)	1% every 1 to 2 hours[26]
Systemic	Prednisone (oral)	30 mg twice a day[24]
	Fluoroquinolones (gatifloxacin)	400 mg twice a day[19]

Table 3. Advantages and disadvantages of vitrectomy in endophthalmitis[23]

Advantages	Disadvantages
Best technique for culture	Associated with delay in arranging operating theatre, etc
Removal of organisms and toxin	May cause retinal detachment or other complication associated with surgery
Ease of intravitreal injection	Decreased half-life of intra-ocular antibiotic
Restoration of medium clarity	Surgical risks and costs
Enhancement in the circulation of antibiotics in the eye	Intravitreal drug toxicity in vitrectomised eye

Box 2. Techniques of pars plana vitrectomy in endophthalmitis[23]

- Lysis of posterior synechiae or removal of fibrin membrane; anterior chamber washout may be required
- ' Open-sky' vitrectomy may be needed if cornea becomes opaque
- Intra-ocular lenses are usually not removed to aid in visualisation during pars plana vitrectomy, except in fungal endophthalmitis
- Core vitreous humour should be removed; usually no attempt should be made to remove the cortical or peripheral vitreous humour
- Attempt to remove core vitreous humour should continue until retina is visible or a bright red reflex is visible but not if visualisation is inadequate
- Minimal suction should be applied to avoid undue traction on the inflamed and necrotic retina
- Intravitreal injection of antibiotics should be given at the end of vitrectomy

vitreous humours. Gatifloxacin has a broad spectrum of coverage over the bacteria involved in endophthalmitis; it also has a low MIC_{90} (ie minimum inhibitory concentration at which 90% of isolates are inhibited), good tolerability, and excellent bioavailability after oral administration. Gatifloxacin may thus represent a major advance in the treatment and prophylaxis of postoperative endophthalmitis.

Subconjunctival and topical antibiotic therapy

Subconjunctival and topical antibiotics are often used to supplement intravitreal injections, in an attempt to increase the concentration of antibiotics within the anterior segment of the eye. Topical application is associated with very poor vitreous penetration, but subconjunctival administration can reach therapeutic concentrations in the eye, especially in the aqueous humour. Even so, subconjunctival administration is more painful than topical application, and it also carries a greater risk of injury: macular infarction resulting from a subconjunctival injection of gentamicin has been reported.[9] The recommended antibiotic dosages in the various regimens used in the management of postoperative endophthalmitis are shown in Table 2.

Steroid treatment

The early use of corticosteroids, in addition to antibiotics, reduces the destructive effects of the extensive inflammation that accompanies infection in endophthalmitis. Corticosteroid therapy may be administered topically, intravitreally, or systemically. In a prospective trial, Das et al[20] demonstrated that intravitreal dexamethasone helped in the early reduction of inflammation, but that drug treatment did not influence the visual outcome. Shah et al[21] reported that using intravitreal steroids as an adjunct to antibiotic treatment had a detrimental effect, in causing a decrease in visual acuity compared with that of patients who received antibiotic treatment alone without steroid. This finding was different from results of another retrospective trial,[22] which reported a slight visual improvement for patients receiving intravitreal steroids. Thus, the role of intravitreal steroids in the treatment of endophthalmitis remains unclear.

Vitrectomy

Vitrectomy has been used to treat acute postoperative endophthalmitis; its advantages and disadvantages are shown in Table 3.[23] The EVS[24] concluded that immediate vitrectomy was not beneficial for patients with an initial visual acuity of hand movement or better. Among patients with initial light-perception-only vision, the likelihood of achieving a visual acuity of 20/40 or better was increased by 3 times after vitrectomy. The routine approach is a three-port pars plana vitrectomy; some of the steps involved are listed in Box 2.[23] Complications of pars plana vitrectomy include infection, bleeding, cataract, glaucoma, and retinal detachment (which can also be a complication of endophthalmitis).

Treatment of chronic postoperative endophthalmitis

Postoperative endophthalmitis develops insidiously, and accurate diagnosis supercedes urgent treatment. In cases of chronic postoperative endophthalmitis caused by coagulase-negative *Staphylococci* species, intravitreal vancomycin therapy is effective, and capsulectomy or intra-ocular lens exchange is typically not necessary. There is no defined treatment protocol for chronic *P acnes*–

induced endophthalmitis; thus, patients are treated by a variety of methods. Two important retrospective studies, by Aldave et al[27] and Clark et al,[28] demonstrated that the injection of intravitreal antibiotics alone is associated with a very high rate of endophthalmitis recurrence. Pars plana vitrectomy with partial capsulectomy was also shown to be more efficacious than vitrectomy alone. The most effective treatment was vitrectomy, total capsulectomy, and the removal or exchange of the intra-ocular lens. Hence, optimal treatment should include intravitreal vancomycin (1 mg in 0.1 mL) and the consideration of pars plana vitrectomy, capsulectomy, and the exchange or removal of the intra-ocular lens. Because the choice of initial therapy does not seem to affect the final visual outcome,[27] the course of treatment should be determined by weighing the risk of recurrence against the risk of adverse effects of the surgical procedures.

Chronic postoperative fungal endophthalmitis is a very rare condition. Treatment with pars plana vitrectomy and intravitreal amphotericin B (5-10 µg in 0.1 mL) is usually recommended,[29] but the concentration of systemic amphotericin that is needed to manage filamentous fungal endophthalmitis is unknown. In cases of postoperative yeast endophthalmitis (ie infection with *Candida* species), high-dosage fluconazole (400-600 mg/d orally) is beneficial.[30]

Treatment of bleb-associated endophthalmitis

No randomised controlled trial has determined the most favourable treatment regimen for bleb-associated endophthalmitis. Given the different aetiologies and unique spectrum of infective organisms, EVS results should not be extrapolated to the management of post-filtration surgery bleb-associated endophthalmitis. Until culture results become available, treatment with broad-spectrum antibiotics against pathogens associated with blebitis generally results in a good visual prognosis. Chen et al[31] reported that treatments with topical antibiotics, such as vancomycin and ceftazidime, can usually be given in an out-patient setting. Early-onset bleb-associated endopthalmitis can be typically managed as acute postoperative endophthalmitis.[32]

Most cases of bleb-associated infection have a delayed onset, likely because of transconjunctival migration of bacteria through leaking or thin-walled blebs. Hence, the management of leaks in a filtering bleb may have an important role in the prevention of infection.[33] Because organisms causing bleb-associated endopthalmitis are typically more virulent than those causing other forms of endopthalmitis,[6] aggressive therapy is recommended. The visual prognosis is often poor. Immediate pars plana vitrectomy is recommended,[28] along with intravitreal administration of vancomycin and ceftazidime. Initial vitrectomy may result in higher final visual acuity than an initial vitreous tap,[34] but this effect has not been reported consistently.[6] Topical and systemic vancomycin, together with ceftazidime, should also be used, because they are effective against the most likely organisms (*Streptococcus* species and *H influenzae*) and are relatively safe. The role of simultaneously using topical or intravitreal corticosteroids in the treatment of late-onset bleb-associated endophthalmitis remains controversial.

Prognostic factors and visual outcome

Patients who exhibit acute postoperative endophthalmitis tend to have poor visual acuity. The EVS found that 3 months after treatment, 41% of patients achieved 20/40 vision and 69% had better than 20/100 vision. The visual prognosis depends on a number of variables, the most important of which are the initial visual acuity[24] and the virulence of the organisms. Other risk factors that can affect the visual outcome include older age, history of diabetes mellitus, corneal infiltration or ring ulceration, abnormal intra-ocular pressure, rubeosis, absent red reflex, and an open posterior capsule.[24] Despite successful control of the infection, some patients may develop further ocular complications, such as opacification of the capsule, retinal detachment, macular pucker, macular infarction, and expulsive haemorrhage.[35]

In the EVS,[36] retinal detachment occurred in 8% of patients after treatment of endophthalmitis. The rate of retinal detachment was related to the presence of and type of microbial pathogens, initial visual acuity, whether there was an open posterior capsule, age (>75 years), and whether there was an additional early postoperative procedure. It was not related to the initial management (vitrectomy, tap, or biopsy) or the presence of diabetes mellitus. Retinal detachment can be repaired by vitrectomy, scleral buckling, cryotherapy, and laser surgery; excellent vision can be restored in a substantial proportion of patients.[36] The management of retinal detachment in endophthalmitis may be further complicated by the limited visualisation by the physician, inflammation, its effects on the vitreous humour and the retina, and, in some cases, the use of intravitreal gas in the presence of intravitreal antibiotics.

Overall, chronic postoperative endophthalmitis has the best visual prognosis of the three types of endophthalmitis. In two large series,[27,28] the average visual acuity in patients without unrelated causes of vision loss was 20/40 or better. Additionally, the choice of initial treatment and the duration of inflammation did not appear to influence the patient's final vision.

The visual outcome is usually good in cases of blebitis; still, recurrent bleb-related infections remain a risk.[37] The prognosis for early-onset bleb-associated endophthalmitis is the same as that for acute postoperative endophthalmitis. In cases of delayed-onset bleb-associated endophthalmitis, however, the visual outcome is strongly related to the virulence of the infecting pathogen, as well as the delay between onset and treatment.[38] The prognosis is poor, despite prompt and successful treatment of the infection.[6]

Box 3. Common prophylactic treatments used to prevent bacterial endophthalmitis from cataract surgery[39]

Prophylactic intervention	Clinical recommendation*
Postoperative subconjunctival antibiotic therapy	C
Preoperative lash trimming	C
Preoperative saline irrigation	C
Preoperative povidone-iodine antisepsis	B
Preoperative topical antibiotic therapy	C
Irrigating solutions containing antibiotics	C
Intra-operative heparin	C

* **In this classification system, interventions graded 'A' are considered very important or crucial to clinical outcome, those graded 'B' are moderately important, and those graded 'C' are of questionable use**

Prophylaxis

In a review of the literature published between 1966 and 2000, Ciulla et al[39] assessed prophylactic treatments for bacterial endophthalmitis that are commonly used in cataract surgery (Box 3). Only preoperatively administered povidone-iodine preparations could be moderately important to the clinical outcome. Other measures were considered possibly relevant, but definitely not related, to the clinical outcome. Thus, more research is needed to validate currently used prophylactic techniques, as well as to search for new ones. Patient education about the early symptoms of infection is the current approach used to minimise the likelihood of developing bleb-related endophthalmitis. Patients with conjunctivitis or blepharitis should seek treatment promptly and avoid wearing contact lenses, especially soft ones.

Conclusion

Endophthalmitis continues to be a serious complication of intra-ocular surgery. The EVS has recognised the role of systemic antibiotic therapy and initial vitrectomy in the management of acute postoperative endophthalmitis. The role of steroids, systemic fluoroquinolones, and the choice of antibiotic against gram-negative bacteria, however, are still controversial and need further study. Moreover, the management of chronic postoperative and bleb-associated endophthalmitis has not been standardised. No conclusive findings on the efficacy of the various prophylactic measures are available. Thus, the treatment and prevention of postoperative endophthalmitis remain a clinical challenge.

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