Taraprasad Das
Editor

Endophthalmitis

A Guide to Diagnosis and Management

Forewords
Harry W. Flynn Jr.
Narsing A. Rao

Springer

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Foreword 1

Endophthalmitis is an important sight-threatening complication with multiple etiologies. Early diagnosis and treatment may help in achieving good anatomic and visual outcomes in these patients. The purpose of this book is to provide clinically useful information which will help clinicians, fellows, and residents in decision making and the management of patients with endophthalmitis. All the authors of this book are well-known in their respective fields and have provided focused discussion on various endophthalmitis issues.

Part I of this book provides insight into the clinical features, epidemiology, differential diagnosis, and management of endophthalmitis with respect to different geographical areas of the world. Part II has chapters dedicated to specific endophthalmitis scenarios. Part III to V describe pharmacology, microbiology, and pathology in detail. Discussion of prophylaxis and clinical trials is elaborated in Parts VI and VII of the book. All the book chapters have been carefully edited by Dr. Taraprasad Das (vice chairman) of the LV Prasad Eye Institute who is a widely recognized vitreoretinal expert.

Endophthalmitis: A Guide to Diagnosis and Management will be a valuable resource for clinicians in the management of endophthalmitis.

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Foreword 2

It is a great pleasure to write foreword for the book *Endophthalmitis: A Guide to Diagnosis and Management* edited by the globally recognized expert on intraocular infections, Dr. Taraprasad Das. This is a comprehensive book on a dreaded complication in the ophthalmic field. By virtue of contributions from experts in the field of diagnosis and treatment of endophthalmitis, it provides state-of-the-art current and evolving surgical and nonsurgical interventions in preventing visual loss from infectious endophthalmitis.

The book is unique in presenting in depth exogenous endophthalmitis from cataract surgery, pars-plana vitrectomy, intravitreal drug deliveries, glaucoma filtering procedures, and accidental penetrating injuries. The authors introduce the topics in an orderly fashion with introduction, incidence/prevalence, microbiology spectrum for the above surgical interventions, prophylaxis, and treatment followed by pertinent conclusions. Importantly, several chapters include global trends in prophylaxis and specific antimicrobial use in cataract surgery.

The orderly presentation of each chapter allows readers to grasp clinically relevant details, controversies in prophylaxis and treatment, and geographic variations in current endophthalmitis management. The presence of several tables and graphs highlighting a spectrum of infectious agents in various surgically related exogenous endophthalmitis is helpful to both clinicians and microbiologists in establishing a proper etiologic diagnosis and antimicrobial treatment options. Moreover, the chapters providing critical reviews of various clinical trials, particularly two-decades-old important endophthalmitis vitrectomy study, help young and established ophthalmologists in understanding the evolution of current treatment modalities of endophthalmitis. Interestingly the chapters emphasize the current relevance of decade-old clinical trials on endophthalmitis and the impact of current improved vitrectomy procedures and recognition of ever-evolving antibiotic resistances in the management of bacterial endophthalmitis.

Congratulations to Dr. Taraprasad Das for assembling the experts who provided the chapters with recent advances succinctly and including tables, graphs, and illustrations. The book will be useful in clinical settings globally for ophthalmologists, internists, ophthalmology residents, fellows, and laboratory personnel in detecting

infectious agents from ocular fluids. The clinicians faced with endophthalmitis should find the book very helpful in patient care to prevent visual loss from intraocular infections.

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Preface

Endophthalmitis is an intraocular inflammation with exudation in the vitreous cavity and an intraocular colonization of microorganisms. It could occur due to any intraocular surgery, trauma, and occasionally infection at the remote site of the body. Post-cataract surgery endophthalmitis is by far the commonest because of the sheer number of cataract surgeries performed in the world. For similar reasons most prospective studies, either for prevention or treatment, have been done in post-cataract surgery endophthalmitis. With better understanding of pathogenesis, availability of superior drugs delivered at site, safer surgical techniques, and technologies, the incidence of endophthalmitis has reduced significantly from 2% in the 1940s to around 0.05% today. Despite these advances endophthalmitis is a dreaded condition that results in increased cost to the patients and to care providers and in loss of vision and/or the eye.

Endophthalmitis. A Guide to Diagnosis and Management is a comprehensive book on the subject. The book has seven sections: General Features, Specific Endophthalmitis, Science of Endophthalmitis Treatment, Prophylaxis and Prevention and Clinical Trials in Endophthalmitis. Each section editor has domain expertise in the subject.

Part I, General Features, comprises of six chapters that deal with the definition, general management, and differentiation from toxic anterior segment syndrome (TASS). Special chapters include the epidemiology and treatment trends in Asia, Europe, and North America. These chapters have documented the current practice of endophthalmitis care in the different continents of the world.

Part II, Specific Endophthalmitis, comprises of 14 chapters that deal with specific endophthalmitis caused by the most common etiology such as intraocular surgery (cataract, glaucoma filtration, penetrating keratoplasty, vitrectomy, intravitreal injection) and trauma and/or most common microorganisms such as fungus, Gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), *Nocardia*, and *Bacillus*. Special chapters deal with endophthalmitis in children and cluster infection.

Part III to V, Science of Endophthalmitis Treatment, comprises of eight chapters that deal with the pharmacology, microbiology, and pathology of endophthalmitis.

Pharmacokinetics of drugs used in endophthalmitis and intravitreal antibiotics in endophthalmitis describe the science and rationality of antibiotic therapy in endophthalmitis. The microbiology section includes the techniques of sample collection and processing, basic microbiology of common infecting microorganisms and the global trends in microbial susceptibility.

Part VI, Prophylaxis and Prevention of Endophthalmitis, comprises two chapters that include the current knowledge and practice of endophthalmitis prophylaxis and the standard of care guidelines for safe intraocular surgery.

Part VII, Clinical Trials, comprises five chapters. Following the basic facts of clinical trials, the results of four clinical trials, two on prophylaxis and two on treatment, are analyzed for their value in clinical practice.

This comprehensive book could have not been possible without the help of all authors and section editors, nationally and internationally. Dr. Naren Aggarwal and Ms. Sowmya Ramalingam from Springer were exceptionally good in shaping the book from concept to production. I owe it all to my patients who not only trusted in my skills but also taught me a lot on the ground. I owe special thanks to Professor Harry W Flynn Jr from the University of Miami and Professor Narsing A. Rao, from the University of South California, the world experts in inflammation, infective endophthalmitis management and eye pathology for writing the forewords. All authors of this book think that the book will be useful to all in-training and practicing ophthalmologists.

Hyderabad, India
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Taraprasad Das, M.D.

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Part I
General Features

Chapter 1
Definition, Signs, and Symptoms of Endophthalmitis

Vivek P. Dave and Taraprasad Das

Introduction and Definition

Endophthalmitis is defined as inflammation of the inner layers of the eye with exudation in the vitreous cavity resulting from intraocular colonization by microorganisms [1, 2]. It is a rare but potentially vision-threatening disease. Unless diagnosed and treated in time, it can lead to severe vision loss. Based on the mode of entry of microorganism, it is divided into "exogenous" and "endogenous." Depending on the causative event, the exogenous endophthalmitis is divided into "postoperative" and "post-traumatic." Based on the time of onset, the postoperative endophthalmitis is divided into "acute" and "delayed" (Fig. 1.1).

Some of the definitions frequently used in endophthalmitis are listed in Table 1.1.

Signs and Symptoms

The classical symptoms of endophthalmitis are increasing pain and reduction in vision (Table 1.2). In the European Society of Cataract and Refractive Surgeons (ESCRS) study [3], the reduction of vision and pain accounted for 92.9% and 79% of all symptoms, respectively, and in the Endophthalmitis Vitrectomy Study (EVS) [4], it accounted for 94% and 74% of all symptoms, respectively. The other common symptoms are a swollen eyelid that usually occurs in infection by more virulent organisms. In the EVS, 82% complained of "red eye"; this symptom was not

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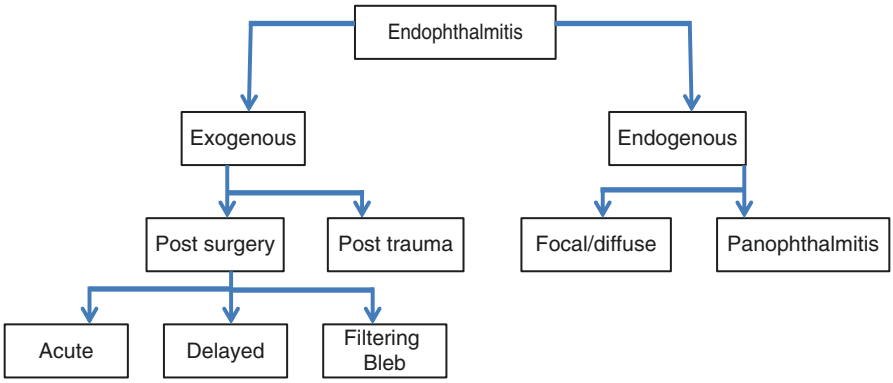

Fig. 1.1 Clinical classification of endophthalmitis

Table 1.1 Definitions of endophthalmitis

Category	Name	Comments
Time [4]	Acute	Endophthalmitis presenting within 6 weeks of surgery
	Chronic	Endophthalmitis presenting after 6 weeks of surgery
Symptoms and signs [5]	Early	An infection with relatively well-preserved media clarity, allowing good red reflex, occasionally even observing retinal details
	Delayed	An infection with severe opacity in the anterior media, typically accompanied by severe vitreous infiltration or true abscess
Microorganism	Bacterial	Gram-positive and gram-negative organisms cause infection
	Fungal	Nonfilamentous or filamentous fungi cause infection
Mode of Entry [2, 3]	Exogenous	The infectious agent reaches the vitreous cavity through external injury, either after intraocular surgery or trauma
	Endogenous	The infectious agents reach vitreous cavity by hematogenous spread

Table 1.2 Common signs and symptoms of endophthalmitis

	Effects	EVS (%) [4]	ESCRS (%) [3]
Symptoms	Decrease vision	94	92.9
	Pain	74	79
	Lid edema	34	46
	Red eye		
Signs	Lid edema	85	72
	Corneal edema		
	Hypopyon, anterior chamber fibrin		
	Vitreous cells		
	Perivascular exudates		

assessed in the ESCRS study. The commonest signs seen are hypopyon and lid edema. In the ESCRS study, hypopyon and lid edema accounted for 72% and 46% of all signs, respectively, and in the EVS, it accounted for 85% and 34%, respectively. Depending on the amount of corneal edema, pupillary membrane, and

vitritis, the indirect ophthalmoscopy may not show a fundal glow but show a mild red glow, or it could be clear enough for visualization of the optic disk and blood vessels.

Additional signs and symptoms may be seen depending upon the etiology of the endophthalmitis. Bleb-associated infections can have prodromal symptoms like headache and brow ache [6]. In traumatic endophthalmitis, the signs of ocular inflammation are usually out of proportion that can be explained by the injury itself [7, 8]. Endogenous endophthalmitis may additionally have floaters and photophobia [9, 10]. As the source of infection in endogenous endophthalmitis is hematogenous, the presentation is often bilateral with systemic morbidity like sepsis, vomiting, nausea, and fever (Fig. 1.2).

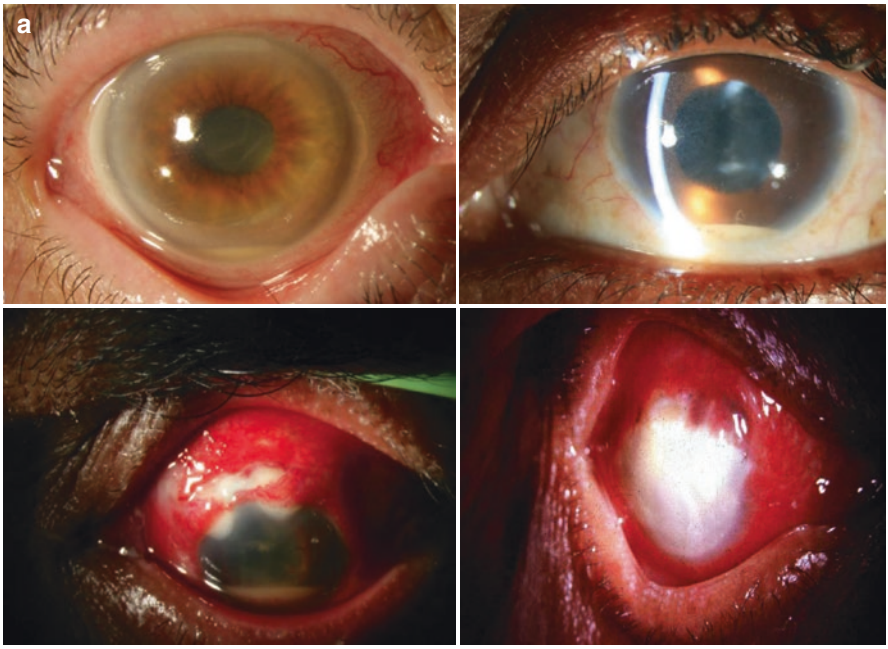

Fig. 1.2 Various presentations of endophthalmitis. (**a**) *Top panel*: *left*, circumcilliary congestion with streak of hypopyon (Courtesy: Harry W. Flynn Jr., MD); *right*, hypopyon and cells in the anterior chamber; causative organism was *Staphylococcus epidermidis* (Courtesy: Tapas R. Padhi, MD). *Bottom panel*: *left*, surgical site infection with exudates and at adjacent corneal periphery; serosanguinous hypopyon in the anterior chamber (Courtesy: Srikant K. Sahu, MD); *right*, anterior chamber filled with exudates obscuring the few of iris, pupil, and other structures; causative organism was *Pseudomonas aeruginosa*. (**b**) *Top panel*: *left*, marked corneal edema, ring infiltrate, and hypopyon (Courtesy: Harry W. Flynn Jr., MD); *right*, fungal endophthalmitis with exudates over iris and pupillary area (Courtesy: Harry W. Flynn Jr., MD). *Bottom panel*: *left*, chronic endophthalmitis with keratic precipitates at the back of the cornea and a streak of hypopyon (Courtesy: Harry W. Flynn Jr., MD); *right*, chronic endophthalmitis with exudates at the back of an intraocular lens (Courtesy: Harry W. Flynn Jr., MD). (**c**) *Top panel*: *left*, delayed endophthalmitis with fibrinous exudates in the pupillary area (Courtesy: Harry W. Flynn Jr., MD); *right*, delayed endophthalmitis with corneal studded with large and small keratic precipitates (Courtesy: Harry W. Flynn Jr., MD). *Bottom panel*: delayed-onset endophthalmitis caused by *P. acnes*—note plaques behind the IOL (Courtesy: Harry W. Flynn, Jr., MD)

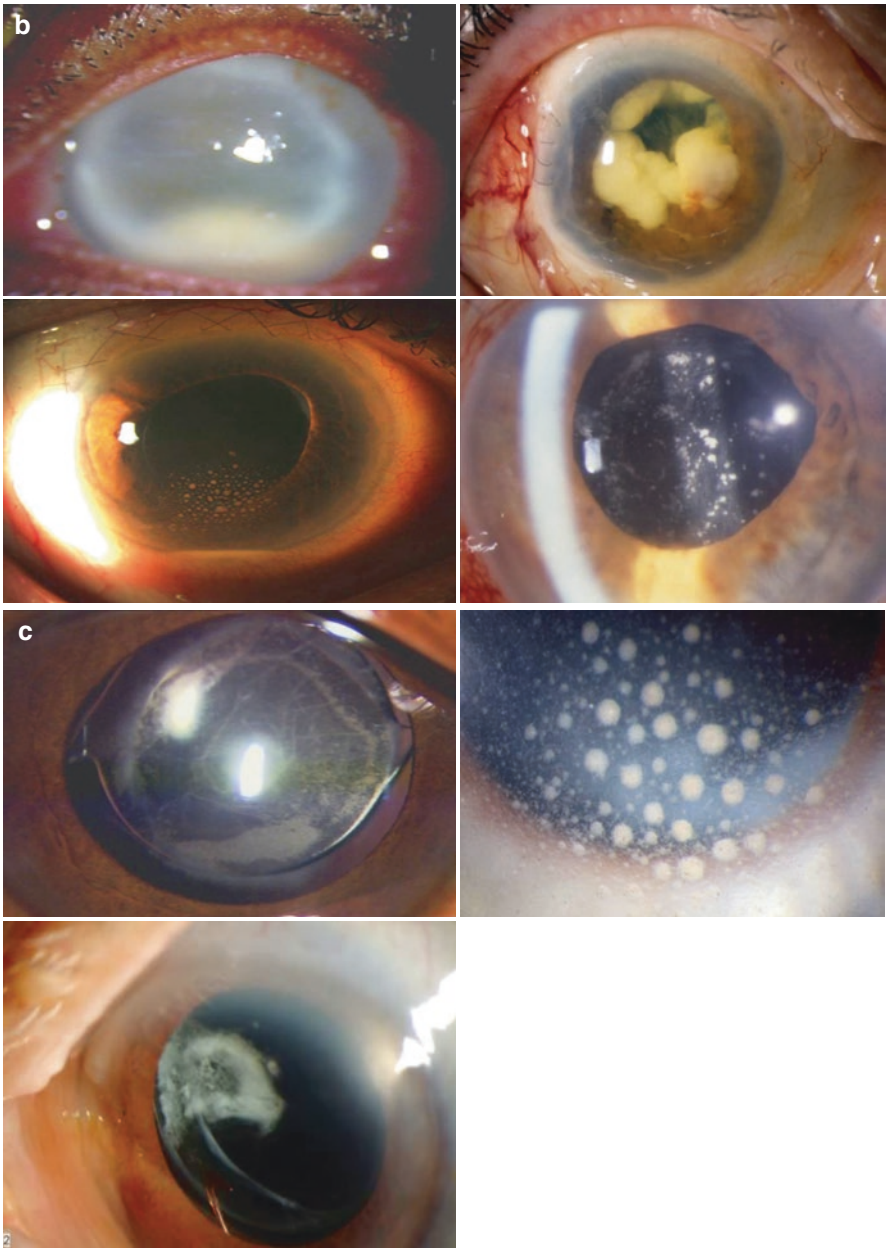

Fig. 1.2 (continued)

The signs and symptoms mentioned above must be documented and frequently monitored to assess progression/resolution of endophthalmitis. Reducing hypopyon, circumciliary congestion, and pupillary membranes and increasing visibility of the fundal glow and retinal vascular details denote resolving endophthalmitis. In contrast, the opposite would indicate that the endophthalmitis is progressing. Occurrence of excessive pain and chemosis should prompt the clinician to look for extraocular motility restriction and proptosis which when present could indicate progression to panophthalmitis and/or orbital cellulitis.

Frequently Asked Questions

1. *How early or late can endophthalmitis occur after surgery?*
   A: Endophthalmitis can occur as early as hours after surgery to as late as years after surgery. Delayed-onset fulminant endophthalmitis is especially a risk in post-trabeculectomy cases where the integrity of the filtering bleb may get compromised over time allowing transit of surface flora into the eye.
2. *Can the eye with endophthalmitis have 20/20 vision?*
   A: Though most cases of endophthalmitis have decreased vision, those that present very early could have 20/20 vision.
3. *I have a post-cataract surgery patient who has been doing well over the first 2 weeks after surgery and now comes with 20/20, N6 vision, mild discomfort, circumciliary congestion, but no hypopyon. How do I rule in/rule out endophthalmitis?*
   A: Most such cases are usually rebound inflammation due to tapering of topical steroids. Ensure that the frequency of topical steroid is commensurate with the expected postoperative inflammation. In all such cases, one should carefully look for early hypopyon by gonioscopy in the inferior angle; also one should look for vitreous cells in the anterior vitreous behind the intraocular lens. If either is present, it is prudent to err on the side of endophthalmitis.

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Chapter 2
Management of Endophthalmitis

Vivek P. Dave and Taraprasad Das

Infectious endophthalmitis is initially a clinical diagnosis made on the constellation of signs and symptoms discussed before. The commonest test beyond clinical examination by slit lamp and indirect ophthalmoscopy is the ultrasonography.

B-scan ultrasound usually shows low- to medium-amplitude vitreous echogenicity and variable amount of choroidal thickening. It can also pick up associated features like retinal detachment, choroidal detachment, or retained intraocular foreign body. In cases with opaque cornea or significant cataract, serial B-scan ultrasound examination is helpful in documenting improvement or worsening by assessing the intensity of the echoes. Though no correlation is seen between the baseline echographic features in endophthalmitis and the infecting organism, the presence of advanced echographic features like dense vitreous opacities, marked vitreous membranes, retinal detachment and choroidal detachment is associated with a relatively poor visual outcome [1, 2] (Figs. 2.1, 2.2, 2.3, 2.4, and 2.5).

Prior to deciding the treatment plan and discussing with the patient (and the family), one must know the following details because it could impact in decision-making:

1. What is the duration between the event (surgery/trauma/systemic disease) and the manifestation? Usually virulent organisms manifest faster than less virulent infection. A chronic infection could be due to a slow-growing organism or even a fungus.
2. In event of trauma, what was the scene of injury? A metal foreign body is different than a vegetative one, and a road traffic injury is different than injury in a relatively clean work place. This helps in suspecting infective organism.
3. Is this bilateral? This could be endogenous in nature.

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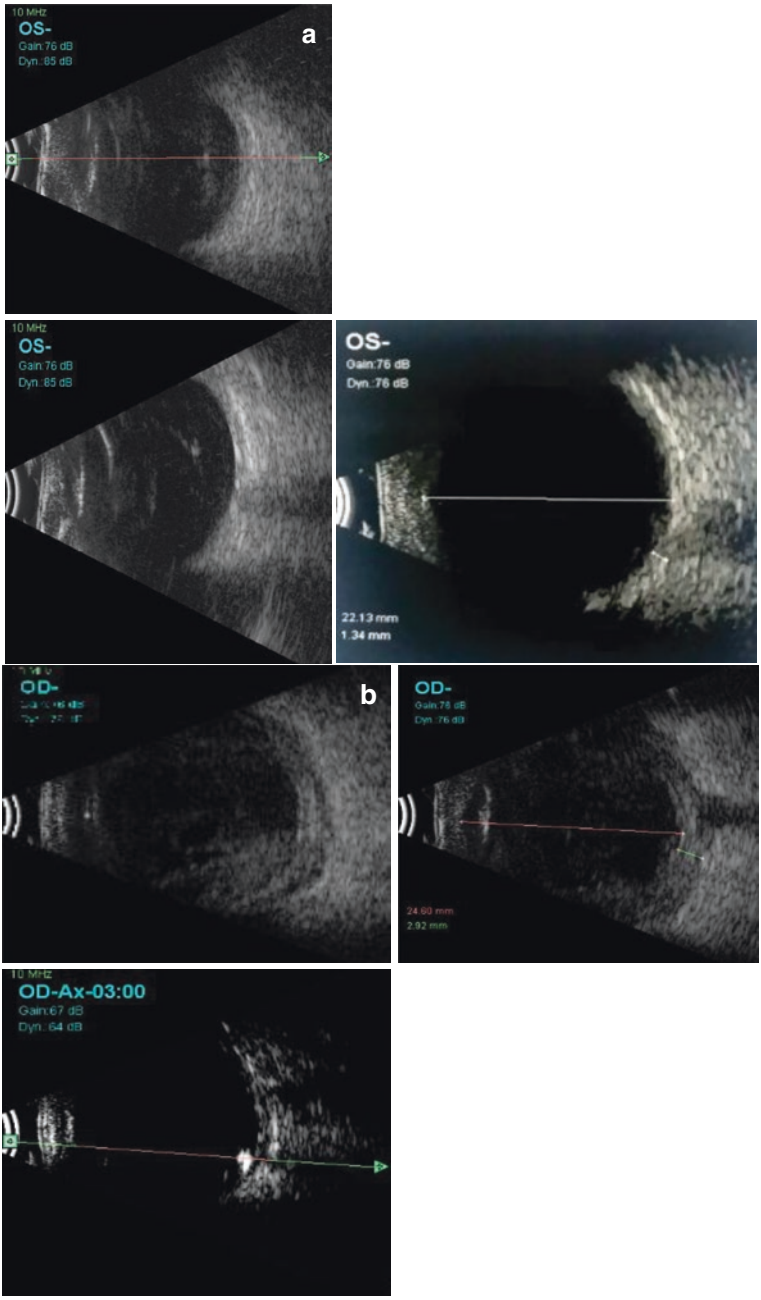

Fig. 2.1 (**a**) *Top*: B-scan in endophthalmitis showing multiple low to medium reflective echoes in the vitreous cavity. *Bottom-left*: B-scan in endophthalmitis showing membrane-like echoes in the vitreous cavity. *Bottom-right*: minimal echoes on B-scan in a case of resolved endophthalmitis. (**b**) *Top*: endophthalmitis progressed to panophthalmitis with vitreous echoes and T-sign suggestive of sub-Tenon's fluid. *Bottom*: endophthalmitis following open-globe injury showing a high reflective echo with posterior shadowing suggestive of a retained intraocular foreign body

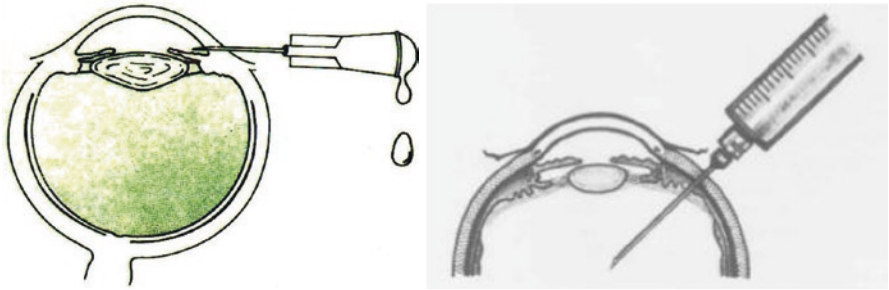

Fig. 2.2 Ocular fluid collection. *Left*—aqueous humor collection; *right*: vitreous humor collection

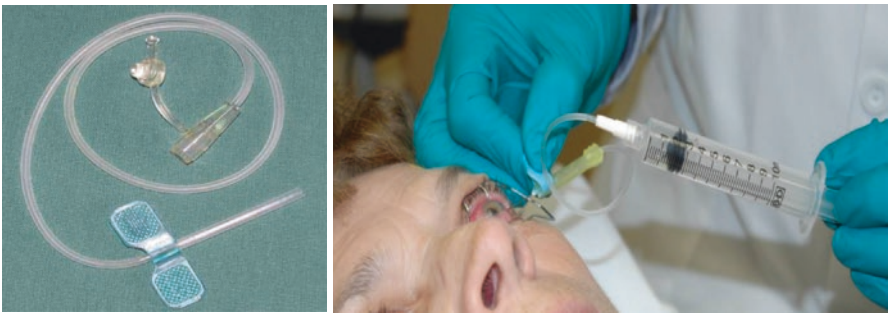

Fig. 2.3 *Left*: butterfly needle. *Right*—vitreous humor collection using a butterfly needle and 10 ml syringe (Courtesy: Harry W. Flynn Jr., MD)

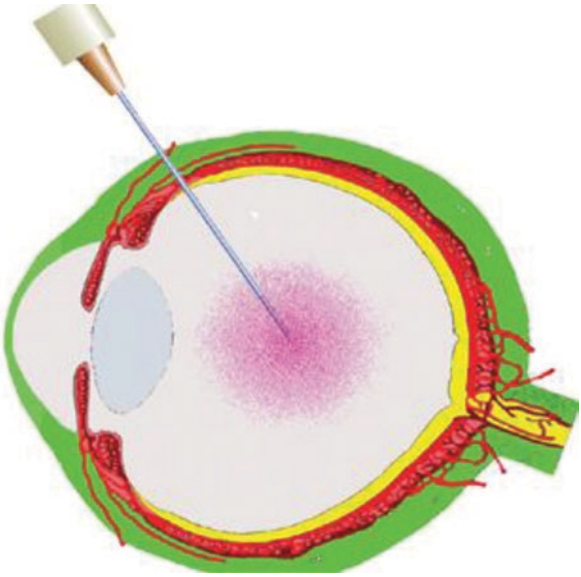

Fig. 2.4 Injection of intravitreal antibiotic into the mid-vitreous cavity

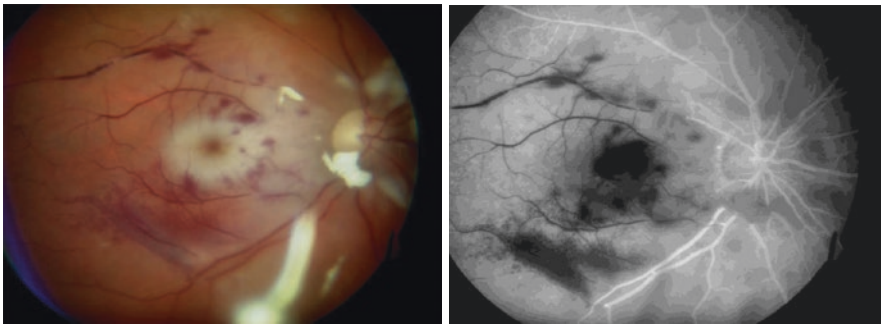

Fig. 2.5 Macular infarction after intravitreal amikacin 0.4 mg in *Staphylococcus epidermidis* endophthalmitis. *Left*—color photo shows attenuated vessels and edema of the posterior pole; *right*: fluorescein angiography shows nonfilling of the posterior pole arteries even in the late phase (Courtesy: Avinash Pathengay, MD)

The First Management Steps

The five essential management principles in management of infectious endophthalmitis are (1) collection of ocular fluid (aqueous/vitreous) specimen for microbiological study; (2) injection of intravitreal antibiotics; (3) intravitreal corticosteroid, when required; (4) vitrectomy, when required; and (5) care of all associated eye injuries.

Collection of Ocular Fluid Specimen

The aqueous humor collection is similar to a paracentesis (Fig. 2.2 left). Following appropriate anesthesia of the eye (usually topical anesthesia) and eye surface sterilized (typically with 5% povidone-iodine), the eye is stabilized with a pair of forceps, and the sample is taken with a small gauge (23–27 gauge) needle attached to a tuberculin syringe. The needle is kept over the iris to avoid trauma to the crystalline lens. It is not ideal to disturb the hypopyon, for fear of creating a tract. A 0.2 ml of fluid is ideal and is processed for microbiology (see the microbiology section of the book).

The mid-vitreous is the ideal location for vitreous humor collection, and when not possible, it is collected from the anterior vitreous. A 0.5 ml undiluted vitreous is ideal. This can be collected manually using a 2 ml syringe or using a vitreous cutter. The eye is anesthetized (usually a peribulbar block), the ocular surface is sterilized (typically, with 5% povidone-iodine), the instrument (needle mounted on a syringe or the vitreous cutter) is inserted in the pars plana region (3.5–4 mm from the limbus), and the required sample is withdrawn for microbiological study. When vitreous surgery is a part of the management, the vitreous fluid is collected using a vitreous cutter. In this case, the vitrector is placed in the mid-vitreous

cavity, and a manual suction could be applied over the aspiration port of the vitrector. In either case, it is necessary that the needle/vitrector tip is visible to the surgeon (Fig. 2.3 right).

A safe vitreous aspiration method has been described using a butterfly needle [3]. In this case the 23 gauge butterfly needle is inserted in the pars plana region to the mid-vitreous cavity, and using a manual suction with a 10 ml syringe, vitreous fluid is collected in the silicone tubing of the butterfly needle system (Fig. 2.3). The collected vitreous sample is sent directly for microbiological processing. This could be safely used for aqueous humor collection.

Intravitreal Antibiotic Injection

Intravitreal antibiotics are given after withdrawal of intraocular fluid, preferably vitreous, or at least aqueous humor, and after vitrectomy, when this is done. The preparation of the antibiotic is described in another chapter (Chap. 22). They are taken in individual syringe and injected slowly in the mid-vitreous cavity with the beveled of the needle pointed to the pupillary area (Fig. 2.4). It is necessary to inject the correct dose of antibiotic, and hence a correct preparation is imperative. Some antibiotics are known to be retina toxic, especially the aminoglycosides, and hence one must not inject the incorrect dose, inject in the mid-vitreous cavity, and take precaution that the drug does not settle on the macula. Two antibiotics are injected, typically one against gram-positive bacteria and one against gram-negative bacteria. In case of fungal infection, only one antifungal antibiotic is injected. The volume of each antibiotic is 0.1 ml, and when required, they could be repeated 36–72 h after the first injection.

Macular infarction is not uncommon with wrong dosage or incorrect method of injection (Fig. 2.5). So as to reduce the dilution error for the commonly used antibiotics (vancomycin, ceftazidime, and voriconazole), the recently introduced E-Kit (Aurolab, Madurai, India; available in India currently) has made the dilution steps easier—add 10 ml of BSS to the antibacterial antibiotic and add 1 ml for the antifungal antibiotic to withdraw 0.1 ml for intravitreal injection [4] (Table 2.1). The current E-Kit contains only four standard intravitreal drugs—two antibacterial antibiotics (ceftazidime and vancomycin), one antifungal antibiotic (voriconazole), and one corticosteroid (dexamethasone) (Fig. 2.6).

Intravitreal Corticosteroid Injection

Dexamethasone is the commonest intravitreal corticosteroid used in endophthalmitis. The intravitreal dose is 0.4 mg in 0.1 ml; it is directly withdrawn from the vial that contains 4 mg dexamethasone phosphate. The details of dexamethasone and other corticosteroid injection are described in another chapter (Chap. 23). Intravitreal

Table 2.1 Traditional and E-Kit dilution steps of three common antibiotics

Antibiotic		Traditional	E-Kit
Vancomycin	Vial size	500 mg	100 mg
	Dilution steps	1. Add 10 ml BSS 2. Withdraw 0.2 ml 3. Add 0.8 ml to make it to 1 ml 4. Keep 0.1 ml	1. Add 10 ml BSS 2. Withdraw 0.1 ml
	Final dose	1 mg in 0.1 ml	
Ceftazidime	Vial size	500 mg	250 mg
	Dilution steps	1. Add 2.2 ml BSS 2. Withdraw 0.1 ml 3. Add 0.9 ml to make it to 1 ml Keep 0.1 ml	1. Add 10 ml BSS 2. Keep 0.1 ml
	Final dose	2.25 mg in 0.1 ml	
Voriconazole	Vial size	200 mg	1 mg
	Dilution steps	1. Add 20 ml BSS 2. Withdraw 0.1 ml 3. Add 0.9 ml to make it to 1 ml 4. Keep 0.1 ml	1. Add 1 ml BSS 2. Keep 0.1 ml
	Final dose	0.1 mg in 0.1 ml	

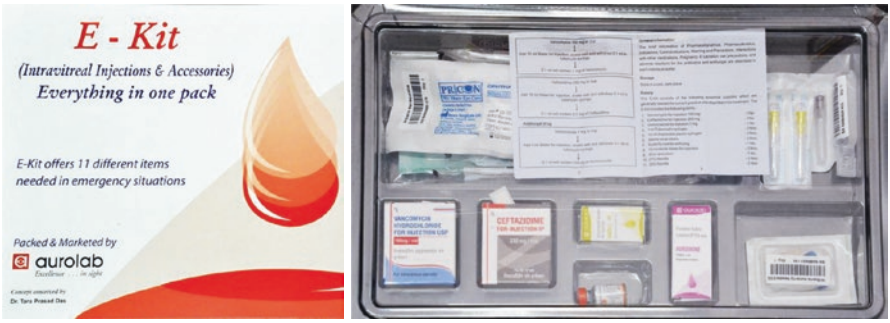

Fig. 2.6 E-Kit

dexamethasone helps reduce the inflammation element in endophthalmitis without compromising the final visual acuity irrespective of the culture positivity [5] (Fig. 2.7).

Vitrectomy

Vitrectomy (Fig. 2.8) is the second key to management of endophthalmitis after intravitreal antibiotics. A three-port vitrectomy is an ideal method of vitrectomy. A longer infusion cannula, such as 6 mm cannula, or use of anterior chamber

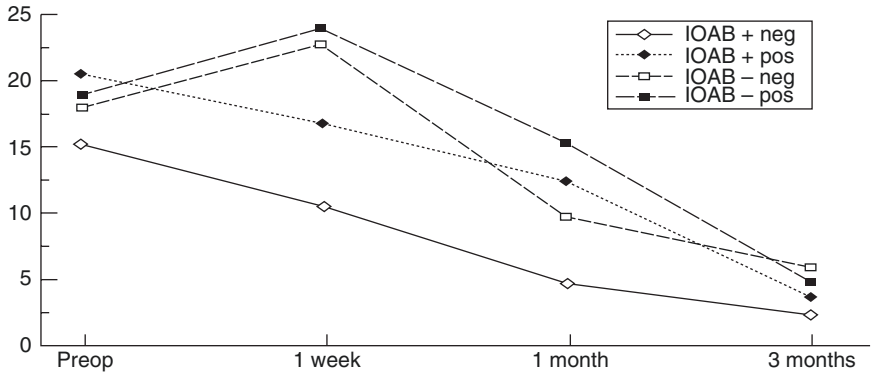

Fig. 2.7 Inflammation is reduced faster in eyes that received intravitreal dexamethasone irrespective of culture positivity, and at end of 3 months, the regained vision was similar to eyes that did not receive intravitreal dexamethasone (Courtesy: Taraprasad Das, MD; reproduced with permission from Br J Ophthalmology 1999; 83: 1050–55)

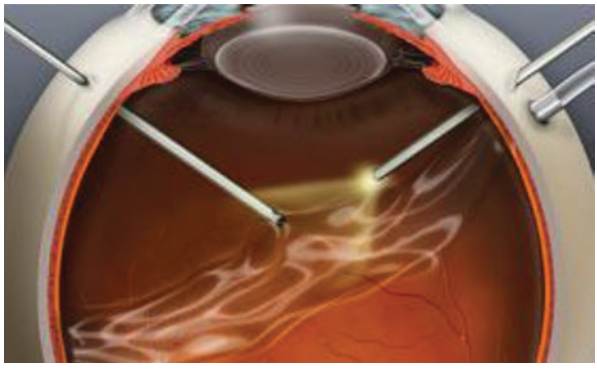

Fig. 2.8 Pars plana vitrectomy in endophthalmitis

maintainer is the safer way to avoid suprachoroidal infusion. Vitreous is collected before the infusion begins, and the tip of infusion cannula must be visualized before the infusion is started. The EVS recommended removal of 50% of vitreous and not to induce posterior vitreous detachment for fear of causing retinal detachment. But with the greater safety of vitreous surgery technique and technology, such as smaller gauge vitrector, more distal position of the cutter port, faster cutting rates, and superior fluidics management have made a complete vitreous surgery in endophthalmitis a distinct possibility.

The Complete and Early Vitrectomy in Endophthalmitis (CEVE) study proposed that if the eye with good red reflex or with some retinal visibility does not benefit from intravitreal antibiotics and intravitreal corticosteroid in 24 h, it should receive a complete vitrectomy regardless of visual acuity [6]. A complete vitrectomy includes separation of posterior hyaloid in the posterior pole, but staying short of the periphery. The rationales of complete vitrectomy are the following: (1)

Table 2.2 Decisions of post-cataract surgery endophthalmitis in China [7]

Period	Tap-inject (%)	Vitrectomy-inject (%)	No intervention (%)
1995–1999	47.0	47.0	6.0
2000–2004	27.5	66.4	6.1
2005–2009	17.8	78.0	4.2

vitrectomy reduces dramatically the inflammatory debris in the vitreous cavity; and (2) vitrectomy reduces the incidence and severity of macular complications. Since the publications of the Endophthalmitis Vitrectomy Study (EVS) over two decades ago, more often the decision is made for vitrectomy-inject than tap-inject. Table 2.2 shows the increasing decisions for vitrectomy over "tap" only in a Chinese study [7].

Adjunctive Systemic Therapy

The EVS used intravenous amikacin and oral ciprofloxacin in people with penicillin allergy, for 5–10 days [8]. But the study did not find any specific advantage and hence did not recommend systemic antibiotics in acute postoperative bacterial endophthalmitis. The good bioavailability of oral moxifloxacin (400 mg twice daily for 5 days) that obtains intravitreal drug concentrations exceeding the minimum inhibitory concentration MIC 90 of most bacteria responsible for endophthalmitis, would merit revisiting the decision of systemic antibacterial therapy [9, 10]. The EVS recommendations do not hold true for other forms of endophthalmitis, such as acute purulent, bleb-associated, posttraumatic, and endogenous endophthalmitis. We recommend systemic fluoroquinolone (typically, oral ciprofloxacin 750 mg twice daily in adults) for 7–10 days in all cases of endophthalmitis.

Repair of Associated Ocular Injury

The repair of associated ocular injury must be done at priority basis. All obvious open-globe injuries should be assessed for the extent of corneal and scleral tear and should be repaired at first intervention. In cases with no obvious tear but evident clinical signs of globe rupture, limbus should be carefully examined for subtle globe rupture. Globe exploration should be done by 360° peritomy to search for an occult scleral tear with meticulous examination including under the insertion of the rectus muscles. An attempt can be made to repair any associated retinal detachment in the same sitting provided visualization permits and the surgeon has adequate clinical experience in the same.

Treatment Options

All cases of suspected or proven endophthalmitis are treated by one of the two methods—(1) tap and inject intravitreal antibiotics and (2) vitrectomy and inject intravitreal antibiotics. The decision to "tap" or perform "vitrectomy" as the first choice depends on the severity of the cases. The EVS recommended "tap-inject" for eyes presenting with hand motions (perception of hand motions at 60 cm) or more and "vitrectomy-inject" for eyes presenting with light perception (LP) or less [8]. Immediate vitrectomy was also advised for patients with diabetes mellitus irrespective of the status of presenting vision. With refinement of vitreous surgery instrumentation, specifically decreased instrument diameter and the safety of working close to the retinal surface, many consider vitrectomy as the first choice in all cases of endophthalmitis irrespective of the presenting vision [6]. Also the modern safety features in vitrectomy system allow one to perform near-complete vitrectomy as opposed to "core vitrectomy" suggested by the EVS. The newest evolution in vitreous surgery is endoscopic vitreous surgery that could obviate the corneal opacity [11].

Explantation an intraocular lens (IOL) is a surgeon-based decision. There are indeed a very few occasions where it is rather mandatory to explant an IOL. Some of these indications include a chronic endophthalmitis not responding to treatment and severe fungal endophthalmitis where the infection has spread anteriorly and involves the IOL.

The standard of care is to inject two intravitreal antibiotics at the conclusion of "tap" or "vitrectomy." This decision is always empirical and is given before the microbiology reports are available. The current recommendations are vancomycin (1 mg in 0.1 ml) that works against gram-positive organisms and ceftazidime (2.25 mg in 0.1 ml) that works against gram-negative organisms. A repeat injection is considered when the culture-antibiotic sensitivity reports are different or there is clinical worsening. The repeat injections can be done safely 48–72 h after the first injection. Antifungal antibiotics are not injected as the primary intravitreal injection unless there is a strong clinical suspicion. Injection of antibiotics into the capsular bag of the crystalline lens is made in cases of chronic endophthalmitis where the infecting microorganisms are suspected to be "sequestered" in the capsular bag.

We recommend intravitreal dexamethasone injection along with the antibiotics as the primary event. This is of course withheld in cases of fungal endophthalmitis.

Associated ocular repair is necessary in bleb-associated endophthalmitis (bleb revision, described in detail in Chap. 8) and in cases of eye trauma. All attempts are made to preserve the crystalline lens in all phakic eyes but must be sacrificed when already injured. IOL implantation is not recommended when the crystalline lens is removed; it is deferred to another time after the infection clears. The treatment algorithm as followed by us in a typical post-cataract surgery acute endophthalmitis is shown in Fig. 2.9 [12].

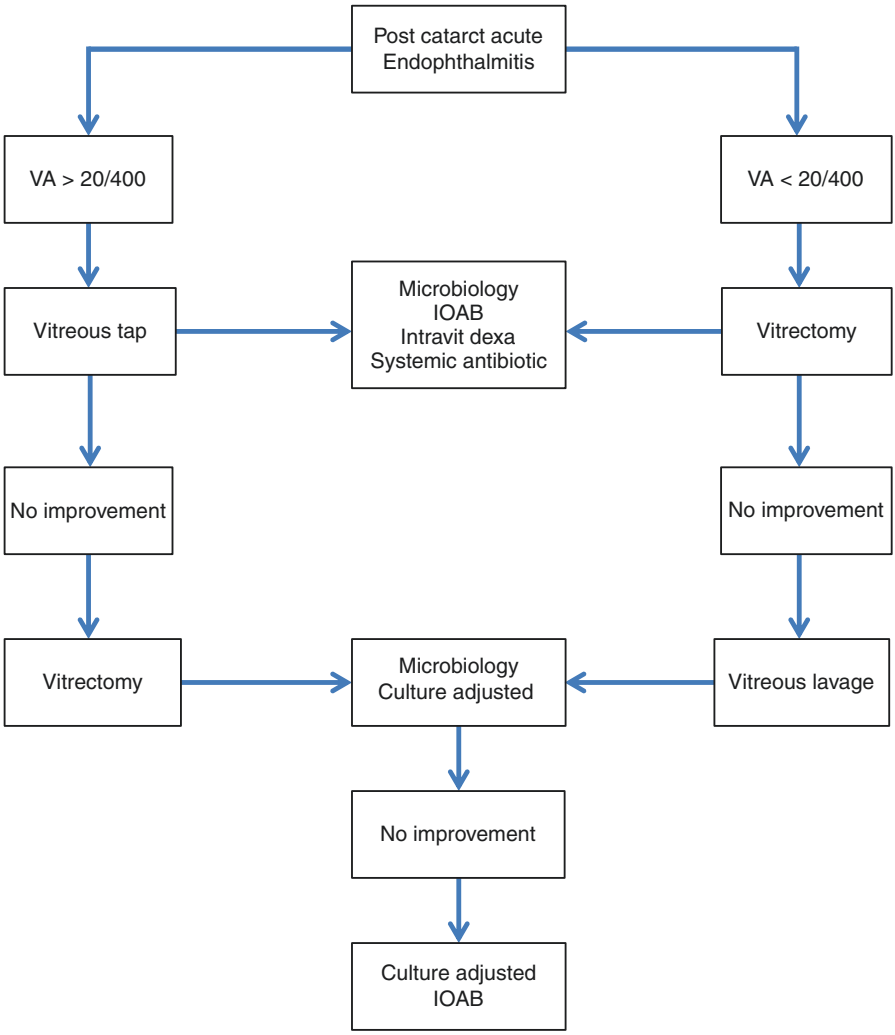

Fig. 2.9 Post-cataract acute endophthalmitis treatment algorithm [12]

Outcomes

The outcome of endophthalmitis care is both anatomical and functional. Many studies have documented outcome after cataract surgery endophthalmitis. We compared our results with the results of the EVS. The settings were not similar. The EVS included only "mild" forms; our cohort included all cases of endophthalmitis. The treatment regimen in our cases included more liberal decisions for vitrectomy contrary to the EVS recommendations for vitrectomy. In the EVS, over 50% eyes

Table 2.3 Visual acuity outcome following treatment for post-cataract surgery endophthalmitis

Visual acuity	EVS (8)	LVPEI [2]
≥20/40	53%	20%
≥20/60	NA	27%
≥20/100	74%	48%
≥20/200	NA	59%
<5/200	15%	NA
No LP	5%	

EVS Endophthalmitis Vitrectomy Study; *LVPEI* LV Prasad Eye Institute, Hyderabad, India

Table 2.4 Visual outcome following post-cataract surgery in China [7]

Period	>20/40	>20/400	No LP
1995–1999	11.2%	40.3%	26.8%
2000–2004	20.2%	57.7%	13.1%
2005–2009	19.2%	71.2%	9.6%

No LP no light perception

regained 20/40 or better, and 5% eyes reduced to no light perception. In contrast, only 20% regained 20/40 or more vision in our study (Table 2.3).

There is also better visual recovery in successive years even in similar setting as shown in a Chinese study [7] (Table 2.4).

Future Challenges

Though over the years the diagnoses and treatment outcomes of infectious endophthalmitis have improved, some inherent hurdles prove a challenge even today. The biggest challenge is the current culture negativity rate, which, in spite of prompt microbiological evaluation, can be as low as 35–40%. Culture negativity causes an inability to get antibiotic sensitivity patterns that usually guide treatment. Secondary sequelae following endophthalmitis like retinal necrosis and retinal detachment are very difficult to manage and invariably lead to loss of functional vision and often phthisis.

The change in the spectrum of microorganisms causing the infections and emerging antibiotic resistance is a great challenge. The Western countries report coagulase-negative staphylococci as the commonest organisms in post-cataract surgery endophthalmitis, minimal gram-negative infection, and almost unknown fungal etiology. In contrast, the Asian and Indian literature reports a high incidence of gram-negative and fungal etiology causing endophthalmitis. These cases have poorer prognosis due to high virulence of the organisms and relatively complicated presentations with corneal involvement that is often a poor prognostic factor.

Frequently Asked Questions

1. *I had an endophthalmitis which was appropriately managed. Now the media is completely clear, and optic disk does not show gross pallor, but the vision is still very poor on final refraction. What to do?*
   A: Assess the fovea on slit lamp biomicroscopy and with an optical coherence tomography. Most such cases which do not improve optimally have a chronic cystoid macular edema. An accompanying fundus fluorescein angiography to assess macular perfusion adds to the information. In an ischemic macular edema, the guarded visual prognosis should be explained. In case the macula is well perfused, intravitreal anti-VEGF or steroids can be attempted with due discussion with the patient about the pros and cons.

2. *Is there a way to suspect microorganism-specific infection?*
   A: There is no foolproof clinical examination modality to identify a specific microorganism in endophthalmitis. Certain clinical features and demographics may suggest a particular organism. Acute post-cataract surgery endophthalmitis is usually caused by coagulase-negative staphylococci. In post-surgical cases following corneal tissue transplants or fulminant host corneal infiltrates, a gram-negative etiology is suspected. Associated nasolacrimal duct blockade often suggests infection with pneumococci. *Bacillus* species especially *Bacillus cereus* is a common etiology following open-globe injuries. In a filtering bleb-associated endophthalmitis, the etiology of acute endophthalmitis is coagulase-negative staphylococci, whereas in a delayed presentation, *Streptococcus* spp. and *Haemophilus influenzae* are commonly seen. Organisms commonly seen in chronic low-grade endophthalmitis include coagulase-negative staphylococci, *Propionibacterium*, and fungi. Fungus species especially *Candida* are the commonest isolates seen in endogenous endophthalmitis especially in immunocompromised and systemically ill patients.

3. *How long should one wait for a second intervention?*
   A: The second intervention is guided by the half-life of the antibiotics injected at the first intervention. The most commonly used empirical antibiotics have a vitreous half-life of about 48 h. Hence a repeat intervention is merited at 48 h. For intravitreal voriconazole, as the half-life is lesser, a repeat intervention is required every 24 h.

4. *What do we infer when the injected antibiotics are not sensitive to the identified microorganism, but the patient is doing well clinically?*
   A: The laboratory reports in endophthalmitis management are a guideline to initiate treatment. The final decision of the treatment is based on the clinical impression. Occasionally, it's possible that the culture plate has picked up a contaminant preferentially which outgrows the actual organism from the biopsy sample. This could also indicate that the organism from the sample is not virulent. The culture sensitivity report in this case may reflect that of the contaminant and not of the one in the sample. Alternately, there could be the same organism with multiple strains of resistance patterns in the same infection. The culture may have grown the resistant ones preferentially, while the vitreous may be harboring the sensitive ones. So continuation of the same treatment is warranted.

5. *What do we infer when the injected antibiotics are sensitive to the identified microorganism, but the patient is not doing well clinically?*
   A: Similar to the previous situation, a possibility of a contaminant should be kept in mind. This situation would warrant a repeat vitreous sampling preferably along with the cassette fluid. One may also consider changing the laboratory to get a correct yield of organisms. In spite of the above if no suitable culture sensitivity patterns are obtained, change the empirical antibiotic combination. One can consider also taking an expert second opinion and a possibility of a noninfectious masquerade.
6. *How do I approach a patient for the fellow eye intraocular surgery where the other eye was successfully treated for culture-positive endophthalmitis?*
   A: Revisit the history and postinfection surveillance report to identify causative factors if any for the previous endophthalmitis. Take adequate precautions to ensure all protocols are adhered to and the deficiencies are corrected. Before taking up the other eye for surgery, ensure patent sac syringing in both eyes, and allow adequate time interval between surgeries to settle the inflammation in the eye treated for endophthalmitis.

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Chapter 3
Toxic Anterior Segment Syndrome (TASS) and Noninfectious Endophthalmitis

Vivek P. Dave

Toxic anterior segment syndrome (TASS) is defined as a sterile postoperative inflammatory reaction caused by noninfectious substances entering the anterior chamber resulting in toxic damage to the ocular tissues [1]. This term was first coined by Monson in 1992 [2]. Those cases that specifically have corneal endothelial dysfunction are separately categorized as toxic endothelial cell destruction syndrome [3–5].

Pathophysiology of TASS

The hallmark of histopathologic feature of TASS is cellular necrosis, apoptosis, and extracellular damage of the intraocular tissues in the anterior chamber of the eye. Though TASS affects the entire anterior segment, the cornea is the most affected tissue since the corneal endothelium is very sensitive to toxic insult. Most of the current understanding of this condition comes from the seminal work of Edelhauser and his colleagues [6–9]. His work concluded that the corneal insult in TASS results in an acute breakdown of endothelial cell junctions. This breakdown causes a loss of barrier function that normally maintains relative dehydration in the cornea; this in turn leads to corneal edema. In mild cases, the surrounding viable corneal endothelial cells compensate for the loss of function overtime and the cornea clears. A permanent corneal damage occurs when the damage supersedes this compensation. TASS can occur due to a variety of reasons (Table 3.1).

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Table 3.1 Causes of TASS [1]

Source	Cause
Irrigating solutions or ophthalmic viscoelastic devices	Incomplete chemical composition • Incorrect pH (<6.5 or >8.5) • Incorrect osmolality (<200 mOsm or >400 mOsm) • Preservatives or additives (e.g., antibiotics, dilating medications)
Ophthalmic instrument contaminants	• Detergent residues (ultrasonic, soaps, enzymatic cleaners) • Bacterial lipopolysaccharides or other endotoxin residues • Metal ion residues (copper and iron) • Denatured OVDs
Ocular medications	Incorrect drug concentration • Incorrect pH (<6.5 or >8.5) • Incorrect osmolality (<200 mOsm or >400 mOsm) • Vehicle with wrong pH or osmolality • Preservatives in medication solution
Intraocular lenses	Polishing compounds • Cleaning and sterilizing compounds

Etiology

Initial reports did not mention any specific etiology for TASS. Bacterial toxins are one of the recently proposed etiologies for TASS [10]. Endotoxins are lipopolysaccharides (LPS) produced by gram-negative bacteria and is a potent inflammatory mediator causing septic shock. The lipid A portion of the LPS molecule is thought to be responsible for this potent inflammatory effect. Endotoxin is heat stable and can readily survive short-cycle sterilization [11]. Bacteria such as *Pseudomonas* are killed by short-cycle sterilization (3.5 min at 180 °C), but their endotoxins are released from the cell walls in the sterilizer. These endotoxins remain biologically active and can be deposited on instruments used in the anterior segment (chiefly, cataract) surgery. Contaminated ultrasonic baths and cleaning detergent liquid has also been implicated [12]. Usage of postoperative ointments can cause the oily substance in the ointments to diffuse into the anterior segment and cause TASS [13].

Clinical Features

The typical hallmark of TASS is an inflammatory process starting in the first 24-h post surgery. The inflammation is classically limited to the anterior segment of the eye. The inflammation in the anterior segment is severe and often results in hypopyon. Another common feature is limbus-to-limbus corneal edema. TASS diagnosis is clinical, and the clinical differentiating features are shown in Table 3.2. Absence of vitreous inflammation is the most significant difference between TASS and endophthalmitis. Three sight-threatening complications of TASS are intractable glaucoma, cystoid macular edema, and corneal decompensation (Fig. 3.1) [1].

Table 3.2 Differentiating features between TASS and infective endophthalmitis

Features	TASS	Infective endophthalmitis
Disease timing	Always, on first postoperative day	Usually, little later unless there is fulminant infection
Pain	Absent	Could be present
Lid edema	Uncommon	Possible
Conj congestion	Minimal	Always
Iris	Fixed, dilated pupil; diffuse iris atrophy	Variable pupil size
IOP	Raised	Variable
Topical steroid	Dramatic response	Temporary response

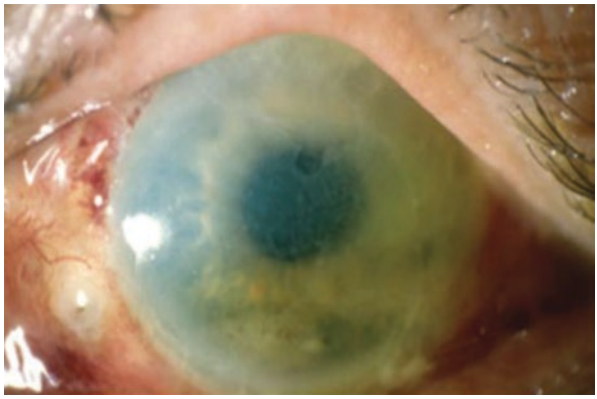

Fig. 3.1 TASS (Courtesy: Harry Flynn Jr, MD)

Management

The TASS cases are noninfective and respond very well to topical steroids. Clinical management hinges on early recognition based on the signs and symptoms as mentioned before. If the picture is unclear, the patient should be treated on the lines of infectious endophthalmitis. Once TASS is confirmed, the mainstay of treatment is topical corticosteroids. The usual regimen is one drop of topical corticosteroid every 30–60 min for the first 3 days with gradual tapering. The response is typically rapid with good improvement. The intraocular pressure should also be monitored closely.

The mainstay of TASS treatment is prevention. The entire surgical team should be aware of all the instruments and chemicals that would be used for a particular case and their sterility. The staff involved in the cleaning and sterilization of instruments should be sensitized to TASS, and it should be ensured that they follow strict protocols to avoid residual disinfectant on the instruments. The use of disposable instruments, as far as possible, is ideal. Both the ultrasound water bath and the steam autoclave should have their water reservoir cleaned daily to avoid contamination. All medications and solutions entering the eye should have their expiry date

cross-checked before use. The solutions should also be checked to ensure that they are of the correct recommended concentration and that they are preservative-free.

In case of an outbreak, an epidemiological investigation should be conducted. The investigation should include the entire team comprising of the surgeon, the scrub nurse, the circulating nurse handling instrument, and the sterilization room staff. All the sterilization procedures and preparation of instruments in the operating room should be assessed to rule out potential source of inflammation. To ensure patient safety, it is prudent that instrument sterilization is as per the protocol mentioned in the instrument manufacturer's instructions. The operating room inventory should have adequate instrument sets to allow proper decontamination and sterilization of the instruments in between surgeries. All the sterilization staff should be well versed with all protocols, and the processes should be regularly audited. As solutions and viscoelastics can dry onto the surface of the instruments quickly, all the instruments should be immediately immersed in sterile water post usage. Phacoemulsification probe could often have material buildup which can be avoided by meticulously cleaning the irrigation and aspiration ports of the handpiece and by flushing the tips and the tubings with sterile water. All gross debris should be removed from the instruments immediately after the surgery under a magnifying lens if necessary. Instruments should be brushed and flushed under water. This helps avoid aerosols that could otherwise contaminate sterile surfaces. Post cleaning, all instruments should be cleaned with oil-free compressed air. Soil deposits from the hard-to-reach areas are best removed by an ultrasonic cleaner. After each use, the ultrasonic cleaner should be emptied, cleaned, and dried. Flash sterilization should be avoided as much as possible.

To ensure that sterilization cycle parameters are well met, a strict documentation of the sterilizer loads should be maintained. For each sterilization cycle, one should document the lot number, the complete contents of the load, the temperature and exposure time, the name of the operator, the result of the indicator put into the load, and any discrepancies in the response of the indicator. Training of new personnel should include verifying the efficacy of training and continued competency in the instrument-processing procedures. Periodic observation of cleaning and sterilization practices by the training personnel and periodic audits of the cleanliness of processed instruments are critical for reducing the risk of TASS.

Noninfectious Endophthalmitis

The diagnosis of infectious endophthalmitis is always clinical. Subsequently a microbiological diagnosis is required by the anterior chamber and vitreous cultures. Although a full-blown endophthalmitis is easy to diagnose, mild cases are many times unclear. Often a subset of patients present with signs and symptoms of endophthalmitis like decreased vision post surgery and mild discomfort. These patients have been shown to comprise a different clinical group termed as noninfectious

endophthalmitis. Lid edema, conjunctival chemosis, and severe pain are conspicuously absent. There can be a small hypopyon or a fibrin coagulum occluding the pupillary axis, but the ultrasound B-scan of the posterior segment is normal with a clear vitreous [14].

All such patients should be treated with intensive topical corticosteroids, initially instilled every half an hour. Cycloplegics can be added in cases that have hypopyon or fibrin coagulum in the anterior chamber. A slit lamp and fundus examination should be done every 4–6 h, and any deterioration in the clinical picture would warrant surgical intervention.

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Chapter 4
Epidemiology and Treatment Trend of Endophthalmitis in Asia

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Asia is one of the most populous continents with a diversity of countries ranging from developing countries like India, Myanmar, and China with a reliance on agricultural economy to developed countries like Japan, South Korea, and Singapore. Infectious endophthalmitis is a rare intraocular infection that results from the introduction of an infectious pathogen into the eye. Acute endophthalmitis is a potentially blinding condition, and prompt recognition and management are critical as this affects the eventual visual outcome. The cause of endophthalmitis is predominantly bacterial or fungal infection, from direct inoculation (exogenous

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endophthalmitis) as a complication of ocular surgery or trauma, through an infected cornea or spread via the bloodstream from a distal source (endogenous endophthalmitis) such as a pyogenic liver abscess or endocarditis. In this chapter, we will review studies on exogenous and endogenous endophthalmitis that highlight the perspective of Asian populations.

Acute Postoperative Endophthalmitis

Postoperative endophthalmitis is a rare but potentially blinding condition, which has been reported to affect 0.04–0.12% of cases in the West [1–9]. Case series from Asian countries have also reported similar incidence of 0.023–0.076% of cases after cataract surgery [10–13]. Besides cataract surgery, it can also occur after glaucoma filtration surgery, vitrectomy, and corneal transplantation [14]. The median time to diagnosis is 5.5 days following surgery with more than two thirds of patients presenting within the first 7 days after surgery [10]. Only 30–50% of these post-cataract surgery cases achieve a final best-corrected visual acuity of 20/40 or better [10, 12].

There is a lower incidence of endophthalmitis in developed countries compared to developing countries (Table 4.1). In Singapore, Saudi Arabia, and Japan, the reported incidence was low, ranging from 0.04% to 0.08% [10, 11, 15, 17, 21, 22]. Studies from Iran, Thailand, Korea, and Taiwan reported a higher incidence that ranged from 0.11% to 0.37% [13, 14, 18–20]. In China, the reported incidence was 0.01–0.03% [12, 16]. The Indian studies have reported an incidence of 0.02–0.09% [23–28].

Table 4.1 Incidence of postoperative endophthalmitis in Asia

Author	Year	Country	Incidence (%)
Jabbarvand et al. [13]	2016	Iran	0.02
Nam et al. [14]	2015	Korea	0.37
Yao et al. [12]	2013	China	0.03
Matsuura et al. [15]	2013	Japan	0.03
Tan et al. [11]	2012	Singapore	0.04
Lin et al. [16]	2011	China	0.01
Al-Mezaine et al. [17]	2009	Saudi Arabia	0.07
Wu et al. [18]	2006 (a)	Taiwan	0.21
Wu et al. [19]	2006 (b)	Taiwan	0.11
Trinavarat et al. [20]	2006	Thailand	0.22
Wong and Chee [10]	2004 (b)	Singapore	0.08
Nagaki et al. [21]	2003	Japan	0.13
Oshika et al. [22]	2003	Japan	0.05

Causative Organisms

Presentation within 6 weeks of surgery is termed acute and beyond 6 weeks as chronic endophthalmitis. This distinction is helpful because the microbiological spectrum causing acute endophthalmitis differs greatly from that causing chronic endophthalmitis. The most common organisms causing acute postoperative endophthalmitis are predominantly gram-positive especially coagulase-negative *Staphylococcus* and less commonly gram-negative *Enterococcus* and *Pseudomonas* species [10, 11, 29] (Table 4.2). Nam reported that *Enterococcus faecalis* and *Staphylococcus epidermidis* were the most common organisms in their series from Korea, but they included infectious endophthalmitis following trauma, corneal and scleral laceration, intraocular foreign body, and endogenous endophthalmitis [14].

The infecting organism predicts the visual prognosis. Eyes with coagulase-negative *Staphylococcus* endophthalmitis and culture-negative endophthalmitis have a better prognosis and are more likely to achieve a better final visual acuity of 20/40 [10]. On the contrary, *Pseudomonas aeruginosa* endophthalmitis tends to result in poorer visual outcomes, with 71% of eyes having final visual acuity of no light perception (NLP) and 50% requiring evisceration [33].

Clinical Features

Postoperative endophthalmitis typically presents within the first postoperative week in approximately two thirds (61%) of cases [34]. Symptoms include eye pain and redness with reduced visual acuity in 75–95% of cases [34]. An afferent pupillary defect may be present in 12%, and eyelid edema, conjunctival injection and chemosis, corneal edema, and anterior chamber inflammation and fibrin accumulation can be observed. A hypopyon is present in up to 86% of cases, and the red reflex is absent in 67% [34] (Fig. 4.1). Other signs include vitritis, Roth spots, vascular sheathing, retinitis, papillitis, and proptosis if it progresses to panophthalmitis.

Prognostic Factors

Eyes with presenting visual acuity of counting fingers (CF) or better and eyes that do not require pars plana vitrectomy are more likely to have a final visual acuity of 20/40 or better [10]. Intraoperative posterior capsule rupture and the use of silicon intraocular lens [10, 12, 13, 35] have been reported to be significant risk factors for endophthalmitis. For unknown reasons, phacoemulsification technique has been observed to have a higher risk of endophthalmitis compared to extracapsular cataract

Table 4.2 Causative organisms in postoperative endophthalmitis in Asia

Author	Year	Country	Coagulase-negative staphylococci	*Staphylococcus aureus*	*Streptococcus* species	*Enterococcus*	Gram-negative organisms	Fungi
Yao et al. [12]	2006–2011	China	32%	12%	4% (*S. pyogenes*)	1%	11%	0%
					4% (*S. viridans*)			
Falavarjani et al. [29]	2006–2011	Iran	38.8%	0%	0%	0%	43.1%	1.5%
Cheng et al. [30]	2002–2008	Taiwan	1%	8%	0%	4%	19%	0%
Kim et al. [31]	2000–2007	Korea	67% (*S. epidermidis*)	11%	11%	11%	0%	10%
Jung et al. [32]	2001–2006	Korea	28% (*S. epidermidis*)	0%	28%	0%	17% (*Enterobacter* sp.)	0%
							17% (*P. aeruginosa*)	
Wong and Chee [10]	1996–2001	Singapore	57%	10%	14%	0%	5% (*P. aeruginosa*)	0%
							14% (other gram-negative)	
							10% (*Serratia marcescens*)	
							33% (*Serratia marcescens*)	

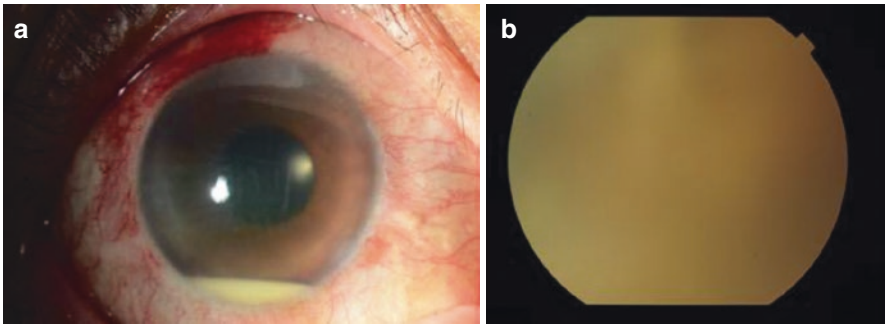

Fig. 4.1 (**a**) A 57-year-old male patient presented with acute postoperative endophthalmitis on postoperative day 5 after phacoemulsification, in-the-bag intraocular lens implant, and capsular tension segment fixation for a right subluxated cataract. Note the congested eye and hypopyon. (**b**) Dense vitritis with hand movement visual acuity with no afferent pupillary defect

extraction, although some other studies do not concur [7, 36]. The use of intracameral cefazolin (1.0 mg/0.1 mL) or cefuroxime (1.0 mg/0.1 mL) has been reported to decrease the rate of endophthalmitis [11, 13], and the incidence of endophthalmitis has also been lowered with prophylactic use of intracameral vancomycin (0.1 mg in 0.1 mL of normal saline) and tobramycin (16 mg/L of irrigation solution) [12]. The associations with age and gender remain controversial [10, 11, 13, 14].

Bleb-Related Endophthalmitis

Bleb-related infections can complicate glaucoma filtration surgery, especially following filtering surgeries with adjunctive mitomycin C with a reported incidence of 1.5% at 2.5 years of follow-up [37]. The most common pathogens identified in bleb-related infections in a prospective multicenter study in Japan were *Streptococcus* species, coagulase-negative *Staphylococcus*, *Haemophilus influenzae*, and *Enterococcus* species among cases with stage IIIb endophthalmitis manifesting with advanced vitreous involvement [38]. Pseudophakic or aphakic eyes tend to be associated with more advanced infection. These cases are associated with deterioration of visual acuity 12 months following the infection—an increase in logMAR visual acuity of at least 0.5 units [39].

Risk Factors

Leaking bleb is a significant predisposing factor for bleb-related endophthalmitis. An inferior quadrant-positioned trabeculectomy has a high risk of developing endophthalmitis. Other risk factors include eyes treated with 5-fluorouracil [40]; the use

of mitomycin C [41]; thin, avascular blebs associated with hypotony; recurrent bleb leakage; pseudophakia; and repeated filtering surgery [42]. The high bleb and blepharitis also increase the risk of endophthalmitis after filtering surgery [41]. In a study from Israel, thin and leaking blebs, long axial length, conjunctivitis, upper respiratory infection, and the winter season were significant risk factors for bleb-related endophthalmitis [43].

Clinical Features

Bleb-related endophthalmitis may present with pain, reduced vision, relative afferent pupillary defect, and hypopyon [43, 44]. Prodromal symptoms such as browache, headache, external eye infection, or inflammation have been observed in previous visits before the onset of bleb-related endophthalmitis [42, 43]. In a study from Saudi Arabia, 89.3% of patients with bleb-related endophthalmitis presented with eye redness, 81.3% had pain, and 22.7% had purulent discharge [45]. The condition may present early within 15 days following surgery or delayed for up to 30 years following filtering surgery [46, 47].

Endophthalmitis After Keratoplasty

The incidence of endophthalmitis post-penetrating keratoplasty is 0.1–0.7% [48]. The predominant pathogens are gram-positive organisms [49]. However, the clinician must also consider fungal pathogens such as *Candida albicans* or *Candida parapsilosis* in the presence of progressive intrastromal opacities around corneal incisions and intraocular inflammation [50].

Endophthalmitis has been reported in 6% (2 of 36 cases) of cases with osteo-odonto-keratoprosthesis (OOKP) surgery. But the case series was small, and one of the cases had endophthalmitis following endoscopic transscleral cyclophotocoagulation a full year after successful OOKP surgery, and the infection was not a direct consequence of OOKP surgery [51].

Endophthalmitis After Intravitreal Injections

Intravitreal injections are now commonly performed for patients with vitreoretinal pathology such as age-related macular degeneration, diabetic maculopathy, and retinal vein occlusion. Several case series have been reported from Asia. The incidence of acute endophthalmitis after intravitreal injections (both in the West and in Asia) ranges from 0.01% to 0.10% [52–55].

Post-traumatic Endophthalmitis

Post-traumatic endophthalmitis may complicate open-globe eye injury. The incidence ranges from 2.1% to 5.1% [56, 57]. The risk of endophthalmitis is significantly higher among eyes with pure corneal injuries, intraocular foreign bodies, traumatic lens rupture, and trauma resulting from needles [57, 58]. Infection by *Bacillus* species (in approximately 25%) can result in rapidly progressive endophthalmitis with a high risk of visual loss due to the destruction caused by cytolysins and enzymes produced by the bacteria [59–61]. Other commonly isolated bacteria include coagulase-negative staphylococcal species such as *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*. The most commonly isolated fungus is *Aspergillus* [62]. *Bacillus cereus* is a major causal organism in post-traumatic cases with poor visual outcome [63].

Chronic Postoperative Endophthalmitis

Chronic postoperative endophthalmitis (CPE) is a rare complication and occurs more than 6 weeks to years after the initial event [64, 65]. The patient typically presents with persistent low-grade anterior chamber inflammation with a characteristic white plaque on the posterior lens capsule and decreased visual acuity in the affected eye. Some patients may experience mild pain, and anterior vitreous inflammation is common [66].

The most common isolated organism in CPE cases is *Propionibacterium acnes* [67], but there are reports of other rare causative indolent organisms such as *Ochrobactrum anthropi* [68], *Massilia timonae* [69], *Mycobacterium manitobense* [70], *Acinetobacter calcoaceticus* [71], *Torulopsis candida* [72], *Corynebacterium minutissimum* [73], and *Alcaligenes xylosoxidans* [74]. With the advent of polymerase chain reaction (PCR), sequencing-based pathogen identification in addition to routine culture methods helps in identifying the microorganisms. Scanning electron microscopy and PCR techniques have demonstrated the adherence of bacteria on the surface of explanted intraocular lens and capsular bags [67, 75].

Endogenous Endophthalmitis

Endogenous endophthalmitis is a rare metastatic ocular infection which can affect both previously healthy and immunocompromised individuals [76]. The medical conditions commonly associated with this are diabetes mellitus, hepatobiliary disease, liver cirrhosis, and malignancy [77–79]. Other underlying associated conditions include renal failure, indwelling catheters, immunosuppressive diseases,

recent surgery, endocarditis, and intravenous drug abuse [76, 80, 81]. Up to 77% have an identifiable causative risk factor [77], and it can affect patients of any age and gender. In Asia, pyogenic liver abscess (PLA) is the most common source [77], and other sources include pneumonia, osteomyelitis, urinary tract infection, soft tissue infection, peritonitis, septic arthritis, catheter-related infection, infective endocarditis, and meningitis [79]. However, the source may remain unidentifiable in up to 7.4–35% of patients despite extensive systemic investigations.

Causative Organisms

Gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae* have been reported to be the most common causative organisms of endogenous endophthalmitis in the West [76, 82]. However, the gram-negative bacteria such as *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* are reported to be responsible for the majority of endogenous endophthalmitis in many case series from Asia [77–79, 81]. Other causative organisms such as *Bacillus cereus* endophthalmitis among intravenous drug abusers, *Haemophilus influenzae* and *Neisseria meningitides* endophthalmitis among pediatric individuals, and *Nocardia asteroides* and *Mycobacterium tuberculosis* endophthalmitis are also reported as rare cases in Asia [80].

Among East Asians, *Klebsiella pneumoniae* has been reported as a common cause of endogenous bacterial endophthalmitis, accounting for approximately 60% of all cases [81, 83]. Hepatobiliary tract infection is a major source of bacteremia (45–62%) [83]; there is a 3.0–7.8% risk of developing endophthalmitis among patients with liver abscess [84–86]. Incidence of endophthalmitis after PLA was estimated to be 0.84%, with a hazard ratio of 12.83 (95% confidence interval 8.94–18.41) compared to patients without PLA [87]. Among patients with liver abscess, diabetes mellitus was reported as a risk of endophthalmitis development and poorer visual outcome [80]. Other reported risk factors include disseminated intravascular coagulation and delayed diagnosis and treatment [81, 83, 88–90]. The interval between the diagnosis of liver abscess and endophthalmitis was approximately 3.12–4.4 days; 4.9–19% of patients presented with ocular symptoms before the diagnosis of sepsis and liver abscess were confirmed [91, 92]. This condition can also affect individuals with no underlying illness or known immunocompromised conditions in 41% of patients [92]. Less commonly, *Klebsiella pneumoniae* endophthalmitis can also arise from renal abscess in diabetic patients [93].

Pseudomonas aeruginosa infection can also present as endogenous endophthalmitis although it is more commonly related to infective keratitis, scleritis, or post-surgical endophthalmitis [33]. Besides gram-negative organisms, gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, group B *Streptococcus*, and *Staphylococcus epidermidis* are most frequently spread from infective endocarditis and skin, bone, and joint infections [79]. One third of the patients may have an underlying chronic disease, such as diabetes mellitus,

underlying malignancy, or acquired immunodeficiency syndrome, but group B *Streptococcus* endophthalmitis can also affect healthy individuals. A reverse relative afferent pupillary defect, sliding hypopyon, and diffuse panophthalmitis can often be observed at presentation as a result of its rapid, widespread destruction of the choroid and retina [94].

Serratia marcescens has been reported to cause irido-lenticular abscess from endogenous endophthalmitis as a result of nosocomial infections in susceptible immunocompromised individuals [95, 96]. Patients can present with intractable pain and angle closure, and high-frequency ultrasound biomicroscopy is needed to detect ciliary body abscesses that may be missed by B-scan ultrasonography. This is an aerobic, gram-negative bacillus that is commonly associated with respiratory and catheter-related bacteremia in susceptible individuals.

Clinical Features

Presenting symptoms of endogenous endophthalmitis are similar to that of postoperative endophthalmitis: ocular pain, reduction of vision, and eye redness [91, 92]. However, certain features have been reported to be characteristic of certain causative organisms, such as a "pupillary hypopyon" with fibrous obscuring the pupil among cases with *Klebsiella pneumoniae* [92], a "sliding hypopyon" among cases with group B *Streptococcus*, and a pink or dark hypopyon with *Serratia* infection. The majority was unilateral although 14–25% of cases may have bilateral involvement [76, 81]. Most patients (up to 87%) had poor visual acuity at presentation (worse than 4/200) [92], and septicemia or an extraocular focus of infection was often present before the presentation of visual symptoms.

Gram-negative organisms commonly present with focal whitish nodules within the choroids or choroidal abscess with rapid involvement of the retina (Fig. 4.2). Intense vitritis is often seen in diffuse severe disease with poor fundal view.

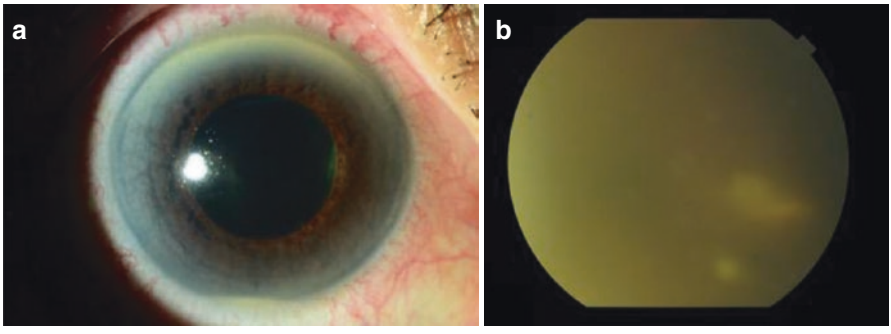

Fig. 4.2 (**a**) A 60-year-old female patient with esophageal carcinoma and liver abscess presented with left endogenous endophthalmitis with (**b**) multiple choroidal abscesses in endogenous endophthalmitis

Perivascular hemorrhages, inflammatory infiltrates, and arterial emboli may be observed [80]. Frank retinal necrosis and globe perforation at the site of an abscess may also occur. In contrast, gram-positive organisms may be multifocal with Roth spots and retinal vasculitis.

The infection can sometimes spread to the orbital tissues and result in panophthalmitis with lid edema, chemosis, proptosis, and limited ocular motility, especially if the infection is caused by *Klebsiella* or *Pseudomonas* species. Another rare presentation is anterior focal disease with discrete foci in iris nodules or microabscesses and mild to moderate anterior segment inflammation.

Visual Prognosis

Many case series reported a poor visual outcome [83, 88, 90, 97] with *Klebsiella pneumoniae* endogenous endophthalmitis, with only 28% having a good final visual acuity (20/120 or better) [81] and 58% of eyes resulting in no light perception [92]. Patients with worse initial vision (worse than counting fingers) typically have poor final visual outcome [83, 91]. Those patients who developed ocular involvement rapidly (<4 days from onset of sepsis) are more likely to develop panophthalmitis [92]. Enucleation or evisceration may eventually be performed in 20–26.8% of eyes [91, 92]. Patients who present with hypopyon and unilateral involvement are more likely to end up with evisceration [92].

Pseudomonas aeruginosa infection has also been reported to have poor visual outcomes, with 71% of eyes having final visual acuity of NLP and 50% requiring evisceration. Primary or secondary pars plana vitrectomy with intravitreal antibiotics achieved a better final visual acuity of 5/200 in 31.3% compared to only 2.2% after nonsurgical treatment with one or multiple vitreous tap(s) and intravitreal antibiotics [33]. Group B *Streptococcus* infection is another devastating condition with eventual loss of light perception and phthisical changes developing in most eyes despite high-dose intravenous antibiotics, intravitreal antibiotic injection, and vitrectomy [94]. A better visual outcome is generally reported for eyes infected with other gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Staphylococcus epidermidis* [79]. *Serratia marcescens* is frequently resistant to multiple drugs, and it has been reported to result in blindness or enucleation in a majority of reported cases [95, 96].

Fungal Endophthalmitis

Fungal endophthalmitis is more common in the developing countries [98, 99], and it can occur via direct inoculation and exogenous or endogenous endophthalmitis [100, 101]. Fungal exogenous endophthalmitis may develop after trauma, ocular surgery, or fungal keratitis in immunocompetent individuals. In contrast,

endogenous fungal endophthalmitis usually occurs in intravenous drug abusers or hospitalized patients, especially those with indwelling catheters.

Fungal endophthalmitis is predominantly endogenous in Korea (82.5%), mostly from *Candida* species (88%) [102]. In contrast, it is mainly exogenous in north China (90.1%) [103], and nearly 60% of the exogenous cases begin with *Fusarium* fungal keratitis. The reason for this trend may be their agricultural lifestyle. Penetrating ocular trauma accounts for another 33%, among which *Aspergillus* predominated among the isolated pathogens. Postoperative fungal endophthalmitis is rare (4%). Half of the endogenous fungal cases in China occur after drug abuse, with *Aspergillus* being the commonest pathogen.

Management of Endophthalmitis

The management of endophthalmitis, exogenous or endogenous, is no different in Asia. It is described in detail in other sections of the book. The incidence of fungal endophthalmitis in Asia is relatively more than the western hemisphere, and hence all care must be taken to include microbiological investigations directed at fungus detection from the beginning and change of intravitreal therapy if fungus is seen in microscopy or it grows in culture. Fungal endophthalmitis also responds to early vitrectomy [102].

Prevention of Postoperative Endophthalmitis

Povidone-iodine has been reported to effectively decrease conjunctival flora in several studies [103, 104] by up to 91%. In addition, intracameral cefuroxime prophylactic regimen at 1 mg in 0.1 mL normal saline was reported to result in a 4.92-fold decrease in the risk of postoperative endophthalmitis in the European Society of Cataract and Refractive Surgeons (ESCRS) multicenter study [105]. While similar benefits were observed in other studies [106, 107], the benefit was minimal in one study [28]. Other Asian studies have reported beneficial effects of intracameral moxifloxacin [15, 108] However, intracameral antibiotic prophylaxis is still not routinely adopted by many ophthalmic surgeon because of the lack of an approved single-unit dose product worldwide that is commercially available, and many are concerned about the potential risk of dilution errors and contamination [109].

Conclusion

Exogenous and endogenous endophthalmitis remain important challenges for clinicians even with an improvement in our diagnostic and therapeutic modalities. The visual outcome is closely related to the virulence of the causative organisms and

potential delay in the diagnosis especially among ill patients who have severe sepsis. Virulent causative organisms like *Klebsiella pneumoniae*, *Pseudomonas*, and group B *Streptococcus* can rapidly destroy ocular tissues, and they are more often reported from Asia. Fungal endophthalmitis is not uncommon in Asian countries, and a more aggressive treatment strategy is required.

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Chapter 5
Epidemiology of Endophthalmitis and Treatment Trend in Europe

Andrzej Grzybowski and Magdalena Turczynowska

Endophthalmitis: Epidemiology

Endophthalmitis is a serious inflammation affecting the vitreous cavity. It is one of the most dreaded complications of ophthalmic surgery, as it may cause severe visual acuity loss, or even loss of the eye in affected patients [1]. Any type of eye surgery could cause endophthalmitis, such as cataract surgery, vitreous procedures (vitrectomy, intravitreal injections), or glaucoma surgery (blebs or implants). The highest incidence of endophthalmitis is observed after secondary IOL implantation and the lowest after pars plana vitrectomy (PPV) in the USA [2]. This is true in other countries too [3]. The incidence for endophthalmitis after cataract surgery in several European countries varies between 0.03% and 0.7% [4–16] (Table 5.1). According to the recommendations of the European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO), maximum acceptable level of incidence for postoperative endophthalmitis after cataract extractions should be 0.05% [17]. ESCRS multicenter endophthalmitis study demonstrated that surgical complications or specific surgery may be related with higher incidence of postoperative endophthalmitis [4]. Higher risk of infection includes patients with clear corneal incisions (versus scleral tunnel incisions) and those with complications at the time of surgery (wound leak, capsular or zonular complication) and without intracameral injection of cefuroxime. Also the type of IOL is considered as a risk factor, with the higher probability of endophthalmitis for silicone versus acrylic (or other material) intraocular lens [4].

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Table 5.1 Endophthalmitis rate after cataract surgery in several European countries

Reference	Country	Publication year	Period	Total *N*	IPOE *N*	IPOE rate (%)	IPOE rate with IC antibiotics	IPOE rate without IC antibiotics (%)
Romero (5)	Spain	2006	2001–2004	7268	25	0.344	0.055% (cefazolin)	0.63
ESCRS (4)	Multiple (EU countries)	2007	2003–2005	15,971	20	0.12	0.05% (cefuroxime)	0.35
Yu-Wai-Man (6)	UK	2008	2000–2006	36,743	35	0.095	0.046% (cefuroxime)	0.139
Garat (7)	Spain	2009	2002–2007	18,579	31	0.167	0.047% (cefazolin)	0.422
Garcia-Saenz (8)	Spain	2010	1999–2008	13,652	42	0.30	0.590% (cefuroxime)	0.043
Barreau (9)	France	2012	2003–2008	5115	36	0.704	0.044% (cefuroxime)	1.238
Friling (10)	Sweden	2013	2005–2010	464,996	135	0.029	0.027% (various)	0.39
Rodriguez-Caravaca (11)	Spain	2013	1998–2012	19,463	44	0.23	0.039% (cefuroxime)	0.59
Beselga (12)	Portugal	2014	2005–2011	15,689	6	0.038	0.00% (cefuroxime)	0.26
Rahman and Murphy (13)	Ireland	2015	2007–2011	8239	5	0.061	0.061% (cefuroxime)	–
Lundstrom (14)	Sweden	2015	2001–2010	692,786	244	0.035	0.03% (various, 99% cefuroxime)	0.43
Creuzot-Garcher (15)	France	2016	2005–2014	6,371,242	6668	0.105	0.046%–0.111% (cefuroxime)	0.080–0.46
Daien (16)	France	2016	2010–2014	2,434,008	1941	0.08	0.06% (cefuroxime)	0.09

IPOE = infectious postoperative endophthalmitis

Table 5.2 Endophthalmitis rate after IVI

Reference	Country	Publication year	Period	Total *N* of IVI	Endophthalmitis *N*	Endophthalmitis rate
McCannel (18)	USA	2011	2005–2009	105,536	52	0.049%
Lommatzsch (19)	Germany	2013	2008–2012	N/a[a]	27	N/a[a]
Tabandeh (20)	Italy and USA	2014	2009–2011	11,710	5	0.043%
Casparis (21)	Switzerland	2014	2004–2012	40,011	3	0.0075%
Fileta (22)	Multiple	2014	2005–2012	350,535	197	0.056%
Brynskov (23)	Denmark	2014	2007–2013	20,293	0	0%
Nentwich (24)	Germany	2014	2005–2012	18,202	3	0.016%
Dossarps (25)	France	2014	2008–2013	316,576	65	0.021%
Ramel (26)	France	2015	2007–2012	11,450	6	0.052%

[a]N/a—no data available

Intravitreal injections (IVI) (mainly of the anti-VEGF agents) are an increasingly commonly performed procedure. In Europe, most of IVIs are performed in the operating room (OR), while in the USA, the vast majority of specialists perform injections in an office setting. The reported incidence for endophthalmitis after IVIs in several European countries does not exceed 0.06% (Table 5.2) [18–26].

Glaucoma surgery (blebs, glaucoma valve placements) also can cause postoperative endophthalmitis. Estimated incidence of bleb-related endophthalmitis (BRE) is <0.1% in case of early-onset and 0.2% for late-onset endophthalmitis [27, 28]. It has been shown that the BRE incidence rate is higher with adjunctive antimetabolites (up to 3%) [29] and when the bleb is placed inferiorly (up to 9.4%) [30].

Endogenous endophthalmitis (EE) is highly uncommon (approximately 2–8% of all cases of endophthalmitis) and is usually associated with other risk factors of systemic infection, such as diabetes, indwelling catheters, intravenous drug administration, malignancy, and immunodeficiency [31]. Because of the rarity, there are no available large-scale studies on the EE etiology, treatment options, and clinical outcomes of these patients.

Endophthalmitis: Etiology

Endophthalmitis may be caused by the microorganisms derived from conjunctival sac, contaminated devices, irrigating solutions, the implanted intraocular lens, or airborne contamination. The Endophthalmitis Vitrectomy Study has shown that in

67.7% of cases with bacterial postoperative endophthalmitis, the intraocular isolates were indistinguishable from the conjunctival and lid specimens [1]. Microbial spectrum of postoperative endophthalmitis varies in different countries and is dependent on environmental, geographical, or climatic factors. Table 5.3 presents the etiology of postoperative endophthalmitis in different regions. Gram-positive bacteria, including *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Streptococcus pneumonia*, are the most commonly isolated organisms from endophthalmitis occurring after cataract surgery in Europe; the gram-negative bacteria represent up to 14% of cases [9, 13, 32, 33]. There are, however, significant differences in a rate of enterococcal infections in Sweden (30–31%) and other European countries (2% in the Netherlands and UK), or the USA (3%). This shift in the preponderance of enterococcal endophthalmitis in Sweden may be connected with widespread use of intracameral cefuroxime and increased proportion of cefuroxime-resistant species. In the USA, as in Europe, the most commonly identified microorganisms are coagulase-negative *Staphylococci* (CONS), whereas the rate of streptococcal infections is lower [34]. In countries such as Taiwan, India, and China, the reported percentage of gram-negative and fungal cases are much higher than in Europe and the USA [35–38]. It has been shown that the bacterial virulence level is the main prognostic factor predictive of the final visual result [39].

Endophthalmitis: Prophylaxis in Cataract Surgery

In 2007 the European Society of Cataract and Refractive Surgeons (ESCRS) published the largest study on perioperative prophylaxis of postoperative endophthalmitis. It was a randomized and controlled multicenter study conducted in 24 ophthalmology units and eye clinics in 9 European countries: Austria (n = 1), Belgium (n = 5), Germany (n = 1), Italy (n = 2), Poland (n = 1), Portugal (n = 1), Spain (n = 4), Turkey (n = 1), and the UK (n = 8). It began in September 2003 and was terminated early in January 2006. The patients were allocated in four treatment groups as it is shown in Fig. 5.1. All groups received povidone-iodine preoperatively and topical levofloxacin postoperatively for 6 days. The study showed that intracameral injection of cefuroxime reduced fivefold risk for contracting endophthalmitis following phacoemulsification cataract surgery [4].

Prophylaxis patterns against infectious postoperative endophthalmitis differ in European countries. In 2013 the European Society of Cataract and Refractive Surgeons (ESCRS) has published guidelines on prevention and treatment of postoperative endophthalmitis [40]. According to this source, it recommends performing surgical procedures in specially prepared operating rooms (proper air flow design, sterile and/or single-used equipment) and hand washing with an antiseptic soap solution, mask, gown, and sterile gloves. Antisepsis of the periocular skin area, cornea, and conjunctival sac with topical povidone-iodine is mandatory. The 5–10% povidone-iodine solution should be left in place at the skin surface for at least 3 min. In case of any contraindications (allergy or hyperthyroidism), the 0.05% solution of

Table 5.3 Pathogens causing postoperative endophthalmitis in different countries

Pathogens	Lundstrom (13) *Sweden*	Friling (9) *Sweden*	Mollan (28) *UK*	Pijl (29) *Netherlands*	Han (30) *USA*	Cheng (31) *Taiwan*	Anand (32) *India*	Kunimoto (33) *India*	Sheng (34) *China*
Gram-positive organisms						44%	37.6%	53%	74%
Staphylococci	35%								
Staphylococcus aureus			5%	12%	10%	24%	8%		12%
Coagulase-negative Staphylococcus (*CoNS*)		26%	62%	54%	70%	3%	13%	33%	46%
Enterococci	30%	31%	3%	2%	2%	12%	2%		7%
Other gram-positive organisms	13.5%	6%	3%	5%	3%	3%	11%		3%
Streptococci		7%	20%	19%	9%	3%	4%	10%	6%
Gram-negative organisms (*Pseudomonas* sp., *Enterobacteriaceae* sp.)	12.5%	14%	7%	6%	6%	56%	41.7%	26%	13%
Negative cultures	16.5%	13%							
Fungi					–		21.8%	17%	13%
Actinomycete-related organisms								4%	

Group A **Placebo vehicle drops x 5*** **No intracameral injection** **Intent to treat** Number of patients: 4054 **Incidence rates (%)** Total: 0.345 Proven: 0.247	**Group B** **Placebo vehicle drops x 5*** **Intracameral cefuroxime injection** **Intent to treat** Number of patients4056 **Incidence rates (%)** Total: 0.074 Proven: 0.049
Group C **Levofloxacin drops 0.5% x 5*** **No intracameral injection** **Intent to treat** Number of patients: 4049 **Incidence rates (%)** Total:0.247 Proven:0.173	**Group D** **Levofloxacin drops 0.5% x 5*** **Intracameral cefuroxime injection** **Intent to treat** Number of patients:4052 **Incidence rates (%)** Total:0.049 Proven:0.025

Fig. 5.1 Study design, total patient numbers, and endophthalmitis incidence rates in each of the four groups in the ESCRS study. *One drop 1 h before surgery, 1 drop half an hour before surgery, 1 drop immediately postoperation, 1 drop 5 min later, and 1 drop 5 min later again

chlorhexidine could be used instead. It is important not to use povidone-iodine solution containing a detergent as it irreversibly coagulates the cornea [40]. ESCRS guidelines recommend applying 1 mg cefuroxime in 0.1 ml saline (0.9%) by intracameral injection at the end of surgery [40].

In 2012 specific commercial cefuroxime sodium at the necessary concentration (0.1 mg/mL) for intracameral use called Aprokam® (Laboratoires Théa, Clermont-Ferrand, France) received approval by the European Medicines Agency (EMA) and was introduced to European market. By now it is officially approved for intracameral antibioprophylaxis of postoperative endophthalmitis after cataract surgery in 24 European countries—Austria, Belgium, Bulgaria, Czech Republic, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the UK (Fig. 5.2). Each vial contains 50 mg of cefuroxime to be reconstituted with 5 ml of saline solution, and it is recommended to administer 0.1 ml into the anterior chamber at the end of cataract surgery. As a broad-spectrum antibiotic, it covers most gram-positive and gram-negative organisms commonly associated with postoperative infectious endophthalmitis: *Staphylococci* and *Streptococci* (except methicillin-resistant *Staphylococcus aureus*, MRSA; methicillin-resistant *Staphylococcus epidermidis*, MRSE; and *Enterococcus faecalis*), gram-negative bacteria (except *Pseudomonas aeruginosa*), and *P. acnes*. In Sweden intracameral cefuroxime is commonly used since 1999 (90% in 2012) and informally recommended by the National Cataract Registry and the Swedish Ophthalmological Society. In France the Health Ministry-governed regulatory Agence Française de Sécurité

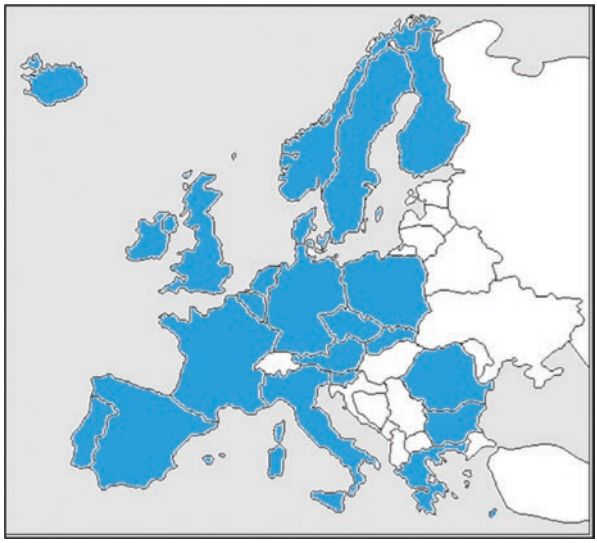

Fig. 5.2 European countries where Aprokam® is nationally authorized

Sanitaire desProduits de Santé in 2011 released official national guidelines that intracameral cefuroxime at the end of the surgery is strongly recommended. In 2011 it was used by 40% of surgeons. In the UK, the Royal College of Ophthalmologists leaves the decision of intracameral antibiotic use to the surgeon, and the Scottish Intercollegiate Guidelines Network recommends intracameral antibiotics in cataract surgery. The surveys from 2010 have shown that it was used by 61% of surgeons then. In the Netherlands, the Dutch Ophthalmological Society recommends cefuroxime in high-risk cases only. In 2010 it was used in 27% of cases. In Italy there are no national guidelines, but surgeons tend to follow the ESCRS guidelines. In 2011 intracameral antibiotics were used in 41% of procedures, either cefuroxime (52%) or vancomycin (48%). In other European countries lacking national guidelines, surgeons also tend to follow the ESCRS recommendations [41].

The use of topical antibiotics differs in many European countries. In Sweden and Denmark, topical antibiotics before and after cataract surgery are not recommended in standard cases by national guidelines, and most surgeons avoid using them. Although postoperative topical antibiotics are used in majority of European countries for 5–7 days, their preoperative use has declined in recent years. For example, the French national guidelines do not recommend the use of topical antibiotics before surgery, and many surgeons in Poland and in Germany stopped this practice in recent years.

The ESCRS guidelines argue that topical antibiotics preoperatively and/or postoperatively do not confer a clear benefit over chlorhexidine or povidone-iodine preoperatively and intracameral antibiotics injected at the close of surgery [40]. However, chlorhexidine has not yet been investigated adequately as prophylaxis for endophthalmitis [42]. Their administration has been shown to reduce the conjunctival

bacterial flora though the addition of topical antibiotics to povidone-iodine does not provide additional reductions in bacterial colonization [43, 44]. It needs to be highlighted that topical antibiotics reduce selected sensitive conjunctival flora, unlike antiseptics, i.e. povidone-iodine that reduces all conjunctival bacterial growth. Furthermore, topical povidone-iodine is the only intervention that has been demonstrated by a RCT to reduce the risk of postoperative endophthalmitis [45, 46]. It is both effective and safe. The choice of postoperative antisepsis is at present a decision of the surgeon, after evaluating the intraoperative complications and postoperative state of the patient. Intravenous antibiotic prophylaxis is not recommended because of weak intraocular penetration in a non-inflamed eye. Oral antibiotic prophylaxis is recommended only in cases of coexisting severe atopic disease when the lid margins are more frequently colonized with *Staphylococcus aureus* [40]. After a penetrating injury, the same antibiotic should be administered systemically, as well as by the intravitreal route [40].

Endophthalmitis: Treatment Guidelines

The ESCRS guidelines on prevention, investigation, and management of postoperative endophthalmitis consider an immediate pars plana vitrectomy performed by a vitreoretinal surgeon as a gold standard of treatment of acute postoperative endophthalmitis [40]. Though the Endophthalmitis Vitrectomy Study (EVS) recommended vitrectomy for patients with light perception only [1], more recent studies have shown that early vitrectomy is beneficial also for patients with better visual acuity [47, 48]. Vitrectomy not only provides an adequate specimen for microbiological diagnostic but also immediately reduces the inflammatory debris in vitreous cavity and removes nontransparent medium allowing inspection of the retina and better access of intravitreally administered drugs to the tissues. Thus, it seems reasonable that the decision to perform surgery should be driven by the clinical appearance and course, than the presenting vision alone.

Samples of infected vitreous should be collected for microbiology examination (Gram stain, culture, PCR), and a combination of either vancomycin 1 mg in 0.1 ml and ceftazidime 2.25 mg in 0.1 ml (first choice) or amikacin 400 μg in 0.1 ml and vancomycin 1 mg in 0.1 ml (second choice) should be administered into the vitreous. Each drug should be injected from separate syringe and 30 G needle. At the same time, 400 μg of preservative-free dexamethasone should be injected into the vitreous. In the case of acute, virulent endophthalmitis systemic therapy with the same antibiotics as those injected intravitreally should be instituted for 48 h. Systemic therapy with corticosteroids (prednisolone 1 or even 2 mg/kg/day) should also be considered. ESCRS guidelines recommends to consider additional systemic antibiotic therapy with the same drugs used for intravitreal injections only in case of severe acute purulent endophthalmitis [40].

When a vitreoretinal surgeon and a vitreoretinal operating room are not available immediately, the silver standard would be a vitreous biopsy with a

vitreous cutter, not with a syringe and needle. Subsequently, antibiotics should be injected intravitreally and repeated as necessary according to the clinical response at intervals of 48–72 h. Full vitrectomy should be considered later [40].

The main prognostic factor predictive of the final visual result in patients with endophthalmitis is bacterial virulence level. Streptococcal strains are often virulent, producing exotoxins, thus associated with poor visual outcome. Accurate diagnosis and prompt treatment are crucial to achieve optimal clinical results with recovery of useful vision.

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Chapter 6
Epidemiology and Treatment Trends in North America

Robert Raut and Derek Kunimoto

Pathogenesis of Endophthalmitis

The intraocular contents are normally sterile and protected from microorganisms by the blood-ocular barrier. However, the vitreous gel can act as a culture medium for microorganisms. Pathogens from the environment as well as normal ocular flora from the patient's biome can lead to infectious endophthalmitis should they gain access to the intraocular space. This may occur from a breakdown of the blood-ocular barrier in endogenous endophthalmitis. Alternatively, the microorganisms may obtain access via wounds breaching the eye wall at the time of surgery, trauma, scleritis, or keratitis, leading to exogenous endophthalmitis.

In North America, bacteria and less commonly fungi or parasites are responsible for exogenous endophthalmitis. They may originate from the rich conjunctival and eyelid flora, from airborne particles or contaminated surgical devices. While not much has been published on the North American patient population recently, the continued understanding is that lid and conjunctival flora remain the main source of pathogens for endophthalmitis caused by access to the intraocular space through an open or incompletely sealed wound. In a prospective study at the New York Eye and Ear Infirmary, 82% of 17 cases of postoperative endophthalmitis showed bacteriological and genetic similarities between microorganisms isolated from the infected vitreous and those isolated from the conjunctiva and lid margin of the patient, in an era before PCR [1].

The normal conjunctival flora in 42 healthy post-WWII San Franciscans mostly consisted of coagulase-negative staphylococci (76% of patients) often coexisting with nonpathogenic *Corynebacterium* (50% of patients). Coagulase-positive staphylococci were present in 10% of patients. *Streptococcus* species were not isolated [2]. Sixty years later, the most common bacteria on conjunctival cultures of

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24 patients at Vanderbilt University, Tennessee, were coagulase-negative staphylococci in 65% of isolates, *Micrococcus* species in 14%, *Staphylococcus aureus* in 9%, gram-negative bacteria in 7%, and *Streptococcus agalactiae* in 2% [3].

This breakdown of conjunctival flora is consistent with pathogens isolated in endophthalmitis series [4–6].

Microbiologic Spectrum of Exogenous Endophthalmitis in North America

Three large retrospective studies have looked at the microbiological spectrum and antibiotic susceptibilities of endophthalmitis-causing pathogens in North American centers over the past decades.

The first study, at Yale in Connecticut, analyzed 143 positive vitreous cultures taken for endophthalmitis between 1988 and 2008. Gram-positive bacteria were identified in 80.6% of isolates, gram-negative bacteria in 12.5% of isolates, and fungi in 6.9% of isolates. The most prevalent organisms in the Yale study were coagulase-negative *Staphylococcus* (37.5%), viridans streptococci (11.3%), *Streptococcus pneumoniae* (6.9%), and *Propionibacterium acnes* (5.6%). While no change in the prevalence of common bacteria was noted over the 20-year study period, rates of staphylococcal resistance to at least one antibiotic tested increased over time. Despite this, no methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant cocci were isolated. All gram-positive bacteria remained sensitive to vancomycin, and all gram-negative bacteria remained sensitive to ceftazidime throughout the study period. Resistance of coagulase-negative staphylococci to gentamicin decreased from 33.3% in the early years of the study to 0% in the later years [4].

The second study, in Florida, looked at all 448 bacterial isolates cultured from vitreous of patients with endophthalmitis at Bascom Palmer from 2002 to 2011. The most common organisms identified were *Staphylococcus epidermidis* in 30.1%, viridans streptococci in 10.9%, *Staphylococcus aureus* in 7.8%, *Candida albicans* in 5.8%, other coagulase-negative staphylococci in 6.0%, *Propionibacterium acnes* in 4.7%, and *Pseudomonas aeruginosa* in 3.1%. Overall, 72.9% of isolates were gram-positive organisms, 10.7% were gram-negative organisms, and 15.8% were fungi. All gram-positive organisms were susceptible to vancomycin, and all gram-negative organisms were susceptible to ceftazidime and levofloxacin. When comparing to vitreous culture results from the same center in the previous decade, susceptibility of both gram-positive and -negative organisms to gentamicin increased, while that of coagulase-negative staphylococci to fluoroquinolones was halved [5].

The third study at the New York Eye and Ear Infirmary looked at the 988 bacterial isolates grown from aqueous or vitreous samples of patients with endophthalmitis, between 1987 and 2011. Overall, 85.1% of isolates were gram positive, 10.3% were gram negative, and 4.6% were fungal. The most common pathogens were *Staphylococcus epidermidis* (30.3%), followed by viridans streptococci species

(12.1%), *Staphylococcus aureus* (11.1%), and other coagulase-negative staphylococci (9.1%). Among the gram-negative organisms isolated, *Enterobacteriaceae* (3.4%) and *Pseudomonas aeruginosa* (2.5%) were isolated most frequently. *Candida* was the most frequently isolated fungus (2.8%). A trend toward the increased prevalence of gram-negative bacteria ($p = 0.08$) and decrease in *Streptococcus pneumoniae* ($p = 0.03$) was observed over the study period. The latter could be attributed to the availability of vaccination against *Streptococcus pneumoniae* and the decline in the use of trabeculectomies in the United States during the study period. Two (out of 727) gram-positive isolates displayed resistance to vancomycin over the 25-year study period, *Enterococcus* in 2005 and *Nocardia* in 2009 [6].

These three studies from Yale, Bascom Palmer, and New York Eye and Ear Infirmary retrospectively analyzed all cases of endophthalmitis submitted to their microbiology laboratories, including postoperative, traumatic, and endogenous etiologies, with little clinical data available on the history of the patients or their visual outcomes. Data on the number of surgical procedures or the antibiotic perioperative regimens was unavailable, as was whether postoperative endophthalmitis cases received povidone-iodine as part of the surgical regimen. Overall, intravitreal vancomycin and ceftazidime administration proved to offer excellent coverage of the microbiological spectrum isolated in those studies. Only at the New York Eye and Ear Infirmary were bacteria resistant to this standard antibiotic treatment isolated. The 0.28% (2 of 727) incidence of vancomycin-resistant bacteria in New York appeared, however, lower than that reported by a similar retrospective study of endophthalmitis bacterial isolates in India where the incidence of vancomycin-resistant bacteria was 1.56% (7 of 448) [7]. Microbiological profile of exogenous endophthalmitis is shown in Table 6.1.

Table 6.1 Microbiological spectrum of exogenous endophthalmitis

	Yale 1998–2008	Bascom Palmer 1996–2001	Bascom Palmer 2002–2012	New York 1987–2001
Authors	Chen 2012 [4]	Schimel 2013 [5]		Gentile 2014 [6]
Coagulase-negative staph	37.5%	37.1%	36.1%	39.4%
S. aureus	4.4%	7.7%	8.0%	11.1%
Viridans streptococci	11.3%	12.8%	10.9%	12.1%
S. pneumoniae	6.9%	–	–	5.2%
P. acnes	5.6%	7.0%	4.7%	8.8%
P. aeruginosa	–	2.2%	3.1%	2.5%
E. faecalis	3.8%	–	–	2.2%
Klebsiella sp.	3.1%	–	–	–
Moraxella sp.	3.1%	–	–	–
H. influenzae	2.5%	–	–	–
Enterobacteriaceae	–	–	–	3.4%
C. albicans	–	2.9%	6.3%	2.8%

Endophthalmitis Following Cataract Surgery

Cataract surgery is the most commonly performed surgical procedure in the United States. The American Academy of Ophthalmology estimates that two million cataract surgeries are performed each year in the United States. In 2010, 1.82 million cataract surgeries were performed on Medicare beneficiaries not enrolled in health maintenance organizations. By comparison, only approximately 250,000 vitrectomies are performed annually in the United States according to the American Society of Retina Specialists (ASRS). Given the large number of cataract surgeries performed, it is easier to study the rare complication of endophthalmitis in cataract surgery than in other less frequently performed eye surgeries.

Incidence

Incidence of post-cataract surgery endophthalmitis in the United States has been investigated with smaller institution-based studies and larger Medicare-based studies. Medicare is a federal health insurance program in the United States. It provides coverage for approximately 50 million Americans, including virtually all people aged 65 years and older and some younger adults with permanent disabilities or end-stage renal disease. A retrospective study was based on a 5% sampling of the 1994–2001 Medicare claims identifying cataract surgeries and subsequent cases of presumed endophthalmitis occurring within the same or next calendar quarter of surgery. The incidence of endophthalmitis in the United States rose from 1.79 cases per 1000 in 1994 to 2.47 cases per 1000 in 2001, an overall increase of 37%. This increase paralleled the adoption of clear corneal wounds from scleral tunnel incisions for phacoemulsification [8]. In another retrospective study based on the Medicare database from 2006 to 2011, out of 2,261,779 cataract surgery cases, 4416 (0.195%) patients were diagnosed with endophthalmitis within 6 months of the surgery. The 0.195% rate from 2006 to 2011 was comparable to the 0.179% rate observed in 1994 in the previous study, prior to the increase to 0.274% in 2001 associated with the adoption of clear corneal wounds. This suggests that with increased experience of creating clear corneal wounds, the rate of endophthalmitis decreased from 2001 to 2006 returning to that observed with scleral tunnels. This study also reports the incidence of fungal endophthalmitis at 0.0005% (121 cases) [9]. A more recent review of 5% of Medicare claims between 2010 and 2013 revealed that 300 patients were diagnosed with endophthalmitis during the year following 216,703 cataract surgeries, which yielded an endophthalmitis rate of 0.14%, also supporting the return of the incidence of this complication at or below the levels seen at the era of scleral tunnels [10]. A smaller retrospective study based in Utah found that endophthalmitis was diagnosed in 26 of 9079 cataract surgeries (0.286%) performed between 1997 and 2001 at the Moran Eye Center [11]. When looking at a longer period in the same center, from 1997 to 2007,

Table 6.2 Incidence of post-cataract endophthalmitis

Author	Years	Number of surgeries	Incidence (%)	Incidence
West 2005 [8]	1998–2001	477,627	0.215	1/466
Du 2014 [9]	2006–2011	2,261,779	0.195	1/512
Jensen 2005 [11]	1997–2001	9079	0.286	1/349
Jensen 2008 [12]	1997–2007	29276	0.157	1/636
Coleman 2015 [10]	2010–2013	216,703	0.14	1/722
Coleman 2015 [10]	2013–2014	511,182	0.06	1/1278

the rate of endophthalmitis decreased to 0.157%, with 46 cases of endophthalmitis out of 29,276 cataract surgeries performed during a 10-year period, once again suggesting that with increased experience with clear corneal wound construction, the incidence of endophthalmitis decreases to a baseline number [12]. The incidence of post-cataract surgery endophthalmitis is shown in Table 6.2.

Microbiologic Spectrum

The majority of cases of postoperative endophthalmitis were caused by gram-positive organisms that are normal flora of the eyelid and conjunctiva. These bacteria may gain access to the intraocular space either through direct inoculation during surgery or due to migration of local flora into an incomplete wound closure postoperatively. In a prospective study consisting of 700 consecutive patients undergoing planned extracapsular cataract extraction, anterior chamber aspirates were culture positive in 14.1% at the beginning and in 13.7% at the end of surgery, despite the use of povidone-iodine 10% antisepsis; coagulase-negative staphylococci and *Corynebacterium* were the most common isolates [13]. In a smaller study on 113 patients undergoing cataract surgery, two patients (1.8%) showed growth in culture of the aqueous humor sampled at the end of the surgery, despite the use of povidone-iodine antisepsis. Fortunately, no patient developed endophthalmitis [14]. These studies suggest that host factors can clear a low inoculum of bacteria in the anterior chamber after cataract surgery without developing endophthalmitis. The increased endophthalmitis rate with posterior capsular defects suggests that the body cannot clear a bacterial inoculum in the vitreous cavity as effectively as in the anterior chamber.

In 1995, the Endophthalmitis Vitrectomy Study addressed the management of endophthalmitis following cataract surgery, which was performed by extracapsular extraction. It remains today the prospective study with the largest number of endophthalmitis patients. Among the 422 patients, vitreous cultures were positive in 69.3% of cases and 9.3% presented with polymicrobial growth. The most common bacteria were *Staphylococcus epidermidis* in 70% of bacterial isolates, *Streptococcus* species in 9.0%, *Staphylococcus aureus* in 9.9%, and enterococci in 2.2%. Gram-positive bacteria represented 94% of isolates, with 5.9% gram-negative species.

Table 6.3 Microbiological spectrum of post-cataract endophthalmitis

	EVS Han 1996 [15] Yield 69.3%	Medicare 2003–2004 Gower 2015 [16] Yield 58%	Bascom Palmer 1996–2005 Lalwani 2008 [17]
Coagulase-negative staphylococci	70.0%	45.0%	68.4%
Staphylococcus aureus	9.9%	–	6.8%
Streptococcus sp.	9.0%	12.0%	8.2%
Enterococcus sp.	2.2%	–	–
Gram negative	5.9%	7.0%	9.6%

All gram-positive species were sensitive to vancomycin [15]. Later studies, during the clear cornea wound phacoemulsification era, reported similar microbiological spectra for endophthalmitis following cataract surgery. A retrospective study of 502 endophthalmitis patients, selected using the 2003–2004 Medicare database, found culture yield to be 58% (lower than 69.3% in EVS), with coagulase-negative *Staphylococcus* in 45% of isolates and *Streptococcus* species in 12% of isolates. Gram-positive bacteria represented 93% of isolates. This study also reported that patients with *Streptococcus* were ten times more likely to have poor visual outcomes than those with coagulase-negative *Staphylococcus*. Worse visual outcomes were similarly noted when comparing patients with gram-negative bacteria to those with gram-positive ones. Finally, a smaller difference in poor visual outcomes was also noted between patients with culture-positive and culture-negative vitreous [16]. Another retrospective study reviewed 73 patients presenting with endophthalmitis at Bascom Palmer, within 6 weeks of cataract surgery from 1996 to 2005. Coagulase-negative staphylococci were isolated in 68.4% of eyes, *Streptococcus* species in 8.2%, and *Staphylococcus aureus* in 6.8%. Worse visual acuity outcomes were noted for infections caused by *Staphylococcus aureus* or *Streptococcus* species compared to those caused by coagulase-negative staphylococci [17]. The uniform microbiologic spectrum in these North American studies may sometimes contrast with the spectra reported on other continents. For instance, an institution-based retrospective study in Taiwan from 2004 to 2015 found that among 32 patients that developed endophthalmitis following cataract surgery, the most common isolates were *Enterococcus* species at 38.1%, *Staphylococcus epidermidis* at 28.6%, and *Staphylococcus aureus* at 9.5% of isolates [18]. Microbiological spectrum of post-cataract surgery endophthalmitis is shown in Table 6.3.

Treatment

Treatment of this sight-threatening disease has historically consisted of administration of intravitreal, subconjunctival, and intravenous antibiotics, with or without intravitreal or oral corticosteroids to minimize inflammatory damage, and drainage of the vitreous abscess by pars plana vitrectomy. The Endophthalmitis Vitrectomy

Study (EVS) is the major landmark evidence-based trial, which established treatment criteria for this condition. This prospective multicenter randomized clinical trial studied the treatment of endophthalmitis developed within 6 weeks of cataract surgery in patients who presented with vision between 20/50 and light perception (LP), without a history of comorbidities which could reduce their visual potential. All 420 patients received intravitreal vancomycin to cover gram-positive organisms and amikacin to cover the gram-negative ones, as well as subconjunctival dexamethasone, vancomycin, and ceftazidime. Patients were randomized to receive additional immediate pars plana vitrectomy or administration of intravenous antibiotics. The results determined that immediate vitrectomy would only benefit patients with LP, while in those with hand motions (HM) or better vision, using intravitreal antibiotics without vitrectomy would provide a similar long-term visual outcome. Moreover, the use of intravenous antibiotics provided no additional benefits to the intravitreal treatment. In the subgroup of diabetic patients, however, those who had HM or better vision also appeared to benefit from immediate vitrectomy as 57% of them achieved 20/40 vision, whereas only 40% did so without vitrectomy [19].

The mainstay of post-cataract endophthalmitis treatment in North America remains close to the one recommended two decades ago by the EVS study. Patients presenting with LP vision or worse undergo emergent pars plana vitrectomy, while those presenting with HM vision or better undergo the less invasive vitreous tap instead. All patients receive empiric intravitreal antibiotic injections, which most often include 1 mg vancomycin to cover gram-positive organisms and 2.25 mg ceftazidime for gram-negative organisms. The latter can be substituted with 0.4 mg amikacin in patients allergic to beta-lactams, although there have been reports of retinal infarction with aminoglycosides at therapeutic dosages. While all patients received subconjunctival antibiotics in the Endophthalmitis Vitrectomy Study, these have been dropped from standard treatment in North America over the past 20 years. In one retrospective study between 1991 and 2002, the final visual outcome of 43 patients presenting with HM vision and acute post-cataract endophthalmitis was similar whether subconjunctival antibiotics were added to the intravitreal ones or not. Moreover, the visual outcomes were comparable to those of the EVS patients [20]. Similar findings regarding the use of subconjunctival antibiotics were reported for treatment of endophthalmitis secondary to trauma, cataract, or glaucoma surgery in a retrospective study of 54 patients treated at Bascom Palmer from 1995 to 2002. This lack of additional effect occurred despite the nonrandomized nature of these trials where the subconjunctival antibiotics may presumably have been used in eyes with more severe disease, as the eyes who did not receive them had a lower rate of enucleation or absent LP outcomes [21]. With the improvement of vitrectomy technology over the past 20 years, allowing safer cutting close to the retina and better intraoperative viewing, more complete vitrectomies are performed, contrasting with the limited vitreous removal suggested in the EVS protocol prohibiting posterior vitreous detachment induction and advising “to remove at least 50% of vitreous gel in eyes with no vitreous separation.” In a consecutive series of 47 eyes, which underwent complete vitrectomy for endophthalmitis with similar

inclusion/exclusion criteria to the EVS, 91% achieved ≥20/40 final visual acuity, as opposed to a 53% rate in the EVS ($p < 0.0001$, Fisher's exact test). No serious adverse effects developed such as retinal detachment and phthisis bulbi or indications for enucleation. There was no case of anatomical failure, as opposed to the EVS with an 11% rate in the nonsurgical group and a 5% rate in the vitrectomy group [22]. Whether early vitrectomy in eyes with hand motions or better vision provides a better outcome by removing harmful agents and inflammatory mediators from the vitreous cavity could benefit from a randomized clinical trial. An indication of expected results could be found in a Medicare-based retrospective study. Across the five states in the study, the use of vitrectomy varied significantly in patients with better than light perception vision. Rates of vitrectomy in such patients ranged from 19% in Michigan to 56% in California, although no evidence was found that this was associated with better visual outcomes [16]. The good bioavailability of oral moxifloxacin following two or five orally administered 400 mg tablets, with obtained intravitreal drug concentrations exceeding the MIC90 (minimal inhibitory concentration in which 90% of isolates were inhibited) of most bacteria responsible for endophthalmitis, would also merit revisiting in future studies addressing the use of systemic antibiotics in the treatment of endophthalmitis [23–25].

Prophylactic Treatment

In order to reduce the risk of endophthalmitis following cataract surgeries, varied treatments have been attempted pre-, peri-, and postoperatively. Given the low incidence of endophthalmitis, an exceedingly large number of patients would be required for a treatment study to be powered to demonstrate a statistically significant effect. A comprehensive review of studies published between 1966 and 2000 found only perioperative povidone-iodine antisepsis to be effective at reducing endophthalmitis rates. Subconjunctival antibiotics, topical antibiotics, antibiotics inside irrigating solution, and lash trimming did not present conclusive evidence of further reducing this risk [26]. Despite this, many American surgeons prescribe antibiotic drops in the pre- and postoperative period in order to reduce the bacterial load and potential inoculum through the surgical wound. A retrospective study at the Moran Eye Center in Utah found topical ofloxacin postoperative use between 1997 and 2001 was more beneficial than ciprofloxacin. While the use of both antibiotics was equal during that period, 85% of endophthalmitis cases developed in patients under topical ciprofloxacin and 15% of them in patients under ofloxacin. The difference between antibiotics was significant ($p < 0.00026$) and may have been due to better penetration of topical ofloxacin into the anterior chamber and a lower kill time for this medication [11]. The replacement of these third-generation agents by newer fourth-generation fluoroquinolone antibiotics prompted a second retrospective study at the Moran Eye Center, from 1997 to 2007. The use of moxifloxacin and gatifloxacin eye drops

from 2003 to 2007 was associated to a lower rate of endophthalmitis of 0.056% when compared with the 0.197% rate under ciprofloxacin and ofloxacin eye drop use from 1997 to 2003 ($p = 0.0011$). When looking at individual agents, the 0.015% rate with gatifloxacin was lower than the 0.1% rate with moxifloxacin ($p = 0.04$) [12]. With the increase in endophthalmitis isolate resistance to fluoroquinolones identified in New York and Florida over the past decades, the benefits of these topical antibiotics as prophylactic treatment may prove to be short-lived however [5, 6]. The use of intracameral cefuroxime at the end of cataract surgery reduced the occurrence of postoperative endophthalmitis by an odds ratio of 4.92 ($p = 0.001$) in a European prospective randomized study of 16,603 patients undergoing cataract surgery from 2003 to 2006. The study reported rates of culture-proven infectious endophthalmitis at 0.07% in the groups receiving intracameral cefuroxime prophylaxis compared with rates of 0.34% in the control groups not receiving intracameral cefuroxime and was stopped ahead of targeted enrolment once this benefit became apparent [27]. Concerns were raised however with the limited coverage against gram-negative bacteria and poor coverage against methicillin-resistant *Staphylococcus epidermidis* and *Staphylococcus aureus*. One consideration to keep in mind is the routine use of intracameral cefuroxime, moxifloxacin, or vancomycin as a prophylactic treatment could lead to increased resistance and sacrifice the benefits of these agents as first-line treatment.

Endophthalmitis Following Pars Plana Vitrectomy

Endophthalmitis is a rare complication of pars plana vitrectomy. Approximately 250,000 vitrectomies are performed yearly in the United States. During the first decade of this procedure (1970–1981) at the Massachusetts Eye and Ear Infirmary, 4 patients (0.137%) with endophthalmitis were reported among the 2917 closed vitrectomies performed. These vitrectomies were performed with 20 gauge or larger instrumentation. All four eyes were lost to this complication [28]. One decade later, from 1985 to 1993, the incidence of endophthalmitis remained low and was reported in 9 patients (0.074%) out of the 12,216 that underwent 20 G vitrectomy in 4 centers across the United States [29]. At Bascom Palmer, 6 cases of endophthalmitis (0.039%) presented following 15,326 pars plana vitrectomies performed between 1984 and 2003. Of these, five cases (83%) had positive vitreous culture growth. All patients resulted in a visual acuity worse than 20/200 and presented virulent bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Proteus mirabilis* [30].

20 G vitrectomy continued to predominate until 2004 when smaller gauge instrumentation became widely available. In the early stages of its adoption, 25 G vitrectomy presented with a higher rate of endophthalmitis than 20 G vitrectomy. In the retrospective analysis of 8601 consecutive vitrectomies performed at the Wills Eye Retina Service, from 2004 to 2006, the incidence of endophthalmitis

was 12 times higher with 25 G procedures (7 of 3103 cases, or 0.23%) than with 20 G procedures (1 of 5498 cases, or 0.018%). The same surgeons performed both procedure types. Indications for surgery in patients who developed endophthalmitis included vitreous hemorrhage and epiretinal membrane, and 50% of patients were diabetic. Incisions with 25 G instruments in this study were not beveled, and all the eyes that developed endophthalmitis were fluid filled at the end of surgery. 25 G vitrectomy was in its earlier phases of adoption at the Wills Eye retina service where approximately 100 cases were performed in 2004, increasing to nearly 2000 surgeries in 2006 [31]. The authors concluded that wound construction and adoption of a new technology likely contributed to the spike in endophthalmitis incidence in 25 G vitrectomy, a conclusion which has borne out with the publication of many subsequent series with lower endophthalmitis rates in 25 G vitrectomy. Another study, published soon after the aforementioned one, provided confirmatory data when it compared 25 G vitrectomy in its early years to the established 20 G procedure. This multicenter, international, retrospective study from 2005 to 2006 reported two cases of endophthalmitis (0.035%) out of 6375 that underwent 20 G surgery, whereas 11 cases (0.84%) out of 1307 25 G vitrectomies did the same. The difference in incidence of endophthalmitis between the different gauge procedures, performed by the same surgeons, in the same settings, was statistically significant ($p < 0.0001$). In the 25 G endophthalmitis eyes, 8 of 11 did not have beveled sclerotomies, and all eyes were fluid filled at the end of the case. Culture yield was 70% in the 25 G cases, and 85% of cultures were positive for coagulase-negative staphylococci. One of the two 20 G endophthalmitis cases grew both staphylococci and *Propionibacterium acnes* in culture. Visual outcomes were variable [32].

With time, however, 25 G vitrectomy displayed lower rates of endophthalmitis comparable to those of the established 20 G procedure. The same international multicenter group retrospectively compared rates of post-vitrectomy endophthalmitis in 2007–2008 among 20 G, 23 G, and 25 G instrumentations. The instrument gauge no longer had an effect on the incidence of postoperative endophthalmitis, which was 1 of 4403 (0.02%) for 20 G vitrectomy, 1 of 3362 (0.03%) for 23 G, and 1 of 789 (0.13%) for 25 G. Comparing these results to those of the same group of surgeons from 2005 to 2006, the incidence of endophthalmitis following 25 G vitrectomies has fallen from 0.84% to 0.13% ($p < 0.056$). The decreased rate of endophthalmitis following 25 gauge vitrectomy in the later series compared to the prior one may be related to increased experience with small-gauge vitrectomy, more complete vitrectomies, adopted use of angled sclerotomy incisions, and more careful closure of the wounds [33]. A similar evolution occurred with the adoption of clear corneal wounds for phacoemulsification. As both the 20 G and 25 G endophthalmitis patients from 2007 to 2008 were left with gas in the eye following vitrectomy surgery, it was unclear if vitreous tamponade had an effect on the rate of endophthalmitis. Table 6.4 lists the endophthalmitis incidence after 20 G and 25 G vitrectomy at different time periods. The incidence of post-vitrectomy endophthalmitis is shown in Table 6.4.

Table 6.4 Incidence of post-vitrectomy endophthalmitis

Author	Years	Gauge	Number of surgeries	Incidence (%)	Incidence
Ho 1984 [28]	1970–1981	20	2917	0.137	1/729
Cohen 1995 [29]	1985–1993	20	12216	0.074	1/1357
Eifrig 2004 [30]	1984–2003	20	15326	0.039	1/2554
Kunimoto 2007 [31]	2004–2006	20	5498	0.018	1/5498
		25	3103	0.230	1/443
Scott 2008 [32]	2005–2006	20	6375	0.031	1/3188
		25	1307	0.841	1/119
Scott 2011 [33]	2007–2008	20	4403	0.023	1/4403
		25	789	0.127	1/709
Garg 2016 [35]	2009–2012	25	14163	0.134	1/745

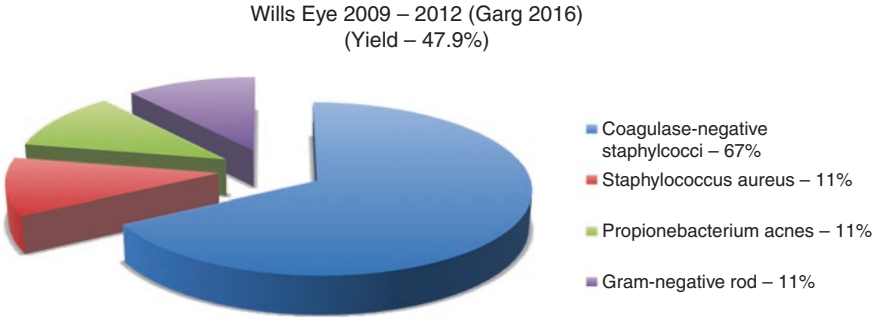

Fig. 6.1 Microbiological spectrum of post-vitrectomy endophthalmitis

In order to help decrease the rate of endophthalmitis following smaller-gauge vitrectomy, a Microsurgical Safety Task Force was formed in 2010 to provide guidelines based on surgical experience if not on scientific evidence. The following steps were believed to be crucial to prevent endophthalmitis [34]:

1. Povidone-iodine preparation
2. Eyelashes completely out of surgical field
3. Conjunctival displacement during entrance into the eye
4. Angled scleral incisions
5. Minimizing vitreous incarceration
6. Wound inspection and suture placement when necessary
7. Perioperative antibiotics

In another, more recent, retrospective study at the Wills Eye Retina Service, from 2009 to 2012, 19 patients (0.134%) presented with endophthalmitis following 14,146 vitrectomy surgeries using 25 G instruments. Culture yield was 47.4% (9 out of 19 patients). Microbial spectrum involved skin flora-associated bacteria, mostly coagulase-negative *Staphylococcus*, followed by *Staphylococcus aureus* and *Propionibacterium acnes* (Fig. 6.1) [35].

Figure 6.1 illustrates the microbiological spectrum of post-vitrectomy endophthalmitis in this study.

Treatment for post-vitrectomy endophthalmitis in the United States does not differ from that of post-cataract endophthalmitis and remains largely based on the findings of the EVS as discussed previously.

Endophthalmitis Following Intravitreal Injections

Intravitreal injections of air were first used in 1911 for the purpose of repairing retinal detachments. Later in the century, they were also adopted for administering intravitreal antibiotics, antivirals, and corticosteroids for endophthalmitis, retinitis, and retinal vascular diseases. The dawn of the twenty-first century saw their use expanded with anti-VEGF agents for the treatment of choroidal neovascularization and macular edema. In 2012, a total of 2.3 million intravitreal injections were performed in the United States. This number was projected to rise to six million in 2016 or twice the annual number of cataract surgeries in the United States.

Microbiologic Spectrum

Commensurate to the number of injections performed, there is a large body of literature on endophthalmitis following intravitreal injection. While most studies addressing endophthalmitis are retrospective in nature, prospective data from clinical trials are also available.

A small meta-analysis of 16 articles published between 2005 and 2009 on endophthalmitis isolates following intravitreal injections in the United States tallied 52 cases following 105,536 injections, resulting in a rate of 0.049%. The most common isolates were coagulase-negative staphylococci at 65.4% and *Streptococcus* species at 30.8%. Streptococci were remarkably more prevalent than following cataract surgery where they represent 8–12% of endophthalmitis isolates. Given that they represent up to 41% of the normal respiratory flora, contamination was presumed to occur not only from the patient's eyelid and conjunctival flora but also from their or the physician's aerosolized upper respiratory biome [36]. A larger meta-analysis of 43 publications between 2005 and 2012 on endophthalmitis after anti-VEGF injections tallied 197 cases following 350,535 injections, or a rate of 0.056%. Positive cultures were obtained in 54% of samples. The most common organisms isolated were coagulase-negative staphylococci in 58%, *Streptococcus* species in 30%, *Staphylococcus aureus* in 5.8%, and *Enterococcus faecalis* in 2.9%. Streptococci were more prevalent and coagulase-negative staphylococci less prevalent than in postsurgical endophthalmitis. This meta-analysis failed to

substantiate a significant difference in visual outcomes between streptococci and staphylococci ($p = 0.22$). The endophthalmitis rate was higher in the prospective studies at 0.068% than in the retrospective studies at 0.053%, although this was not statistically significant ($p = 0.52$). The majority of visual outcome data associated with culture-positive endophthalmitis cases were presented in the retrospective series [37].

A retrospective study at Wills Eye Retina Service from 2009 to 2012 addressed the difference in endophthalmitis after intravitreal injections compared to that following vitrectomy surgery. The former group presented a rate of 0.038% (44 of 117,171 injections) and the latter a rate of 0.134% (19 of 14,146 vitrectomies). Culture yield was similar for both groups with 38.6% of injection cases and 47.4% of vitrectomy cases. The majority of culture-positive cases from postinjection eyes grew oral flora-associated organisms such *Streptococcus* species (35.3%), *Enterococcus* (11.8%), and *Lactobacillus* (5.9%). None of the post-vitrectomy positive culture eyes grew oral flora-associated bacteria. The microbial spectrum in the postinjection cases was significantly different from the post-vitrectomy cases where coagulase-negative staphylococci grew the most, followed by other skin flora-associated bacteria. There were significantly worse visual outcomes in patients with oral flora-caused endophthalmitis in a subgroup analysis of the postinjection patients [35].

A large multicenter retrospective study of 503,890 intravitreal injections performed between 2009 and 2013 reported 183 cases of endophthalmitis or a rate of 0.036%. No significant difference was noted between the three available anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept) in the incidence of endophthalmitis, causative organisms, or final visual outcomes. Positive cultures were obtained in 38% of vitreous and anterior chamber samples. The visual outcome was better in patients with negative cultures than with positive cultures. Among those with positive cultures, visual outcomes were worse following *Streptococcus* infections than they were following coagulase-negative *Staphylococcus* infections. Coagulase-negative staphylococci were the most commonly isolated organisms (52.9%), followed by *Streptococcus* species (24.3%), *Staphylococcus aureus* (7.1%), and *Enterococcus faecalis* (7.1%) [38]. The incidence of post-intravitreal injection endophthalmitis is shown in Table 6.5.

Table 6.6 compares the microbiological profile of endophthalmitis following cataract surgery, following vitrectomy, and following intravitreal injections.

Table 6.5 Incidence of post-intravitreal injection endophthalmitis

Author	Years	Number of injections	Incidence (%)	Incidence
Mccannel 2011 [36]	2005–2009	105,536	0.049	1/2030
Fileta 2014 [37]	2005–2012	350,535	0.056	1/1779
Garg 2016 [35]	2009–2012	117,171	0.038	1/2663
Rayess 2016 [38]	2009–2013	503,890	0.036	1/2753

Table 6.6 Comparison of the microbiological profile of endophthalmitis following cataract surgery, vitrectomy, and intravitreal injections

Endophthalmitis	Study	CONS (%)	*S. aureus* (%)	Strep (%)	Entero (%)	*P. acnes* (%)	GNB (%)	Lacto (%)	*Haemophilus* (%)	*B. cereus* (%)
Post-cat	EVS [15]	70	9.9	9	2.2	–	5.9	–	–	–
	Medicare [16]	45	–	12	–	–	7	–	–	–
	BPEI [17]	68.4	6.8	8.2	–	–	9.6	–	–	–
Post-vit	WEI [35]	67	11	–	–	11	11	–	–	–
Post-intravit inj	Meta [36]	65.4	–	30.8	30.8	–	–	–	–	3.9
	Meta [37]	58	5.8	30	30	–	–	–	1.4	1.4
	WEI [35]	29.4	11.8	35.3	35.3	–	–	5.9	–	–
	Multicenter [38]	52.9	7.1	24.3	24.3	1.4	–	1.4	2.9	–

Post-cataract endophthalmitis: EVS, Endophthalmitis Vitrectomy Study [15]; Medicare 2003–2004 [16]; BPEI, Bascom Palmer Eye Institute 1996–2005 [17]
Post-vitrectomy endophthalmitis: Wills Eye Institute 2009–2012 [35]
Post-intravit injection endophthalmitis: meta-analyses 2005–2009 [36] and 2005–2012 [37]; WEI, Wills Eye Institute 2009–2012 [35]; Multicenter 2009–2013 [38]

Prophylactic Treatment

In the past, some surgeons have performed intravitreal injections in the operating room with similar sterile technique and conditions as incisional surgery, including ventilation systems, masks, sterile gloves and gowns, draping, speculum use, and povidone-iodine scrubs. The sheer volume of intravitreal injections in the United States has led other surgeons out of the operating room to a more efficient examination room setting, increasing access to these treatments while reducing burden on both patients and surgeons. In the office-based setting, povidone-iodine antisepsis, plus or minus the use of speculums and gloves, was carried over, leaving behind the surgical ventilation systems, sterile gloves, gowns, masks, and draping.

Povidone-iodine use remains a cornerstone of the eye preparation prior to intravitreal injections. A retrospective review of 28,786 injections performed during the DRCR network studies, between 2006 and 2015, reported 11 cases of endophthalmitis, or a rate of 0.038%. The use of topical antibiotics made no difference in the rate of endophthalmitis, with a rate of 0.05% reported in eyes receiving them and 0.02% in eyes without ($p = 0.17$). Despite study protocols specifying the exposure of the injection site for 30 s to povidone-iodine, 13 injections in 3 eyes of 2 patients were performed without this agent. One eye in each of those patients developed postinjection endophthalmitis, representing a 15% risk per injection or 100% risk per patient [39].

The use of eyelid speculum has been shown in one large retrospective series to be optional, as long as lid margins are safely kept away from the injection site and needle. A multicenter retrospective study of 27,736 injections performed from 2009 to 2010 in 16 practices associated with the Wills Eye Hospital reported 23 cases (0.083%) of endophthalmitis. Neither the use of a speculum or the hemisphere of injection location affected the risk of endophthalmitis [40]. In a retrospective study of 10,208 intravitreal injections performed at the Massachusetts Eye and Ear Infirmary in Boston, between 2007 and 2011, where 3 cases of endophthalmitis were diagnosed (0.029%), omission of a sterile drape, eyelid speculum, or postinjection antibiotics by several of the treating ophthalmologists did not result in an increased rate of endophthalmitis [41]. Another retrospective study of 10,614 intravitreal injections performed in the Wills Eye clinics, using a manual lid retraction technique instead of a metal speculum, reported 4 cases of endophthalmitis or a rate of 0.03%, similar to that reported in studies where speculums were used [42].

The role of topical antibiotic drops as prophylaxis against endophthalmitis has been debated over the past decade. A prospective study on 24 patients using a 5-day course of topical antibiotics following monthly intravitreal injections found that while the bacterial load was reduced by 41% in treated eyes, *Staphylococcus* populations shifted toward *S. epidermidis* with azithromycin use and toward *S. aureus* with fluoroquinolone use. Exposure to antibiotics increased bacterial resistance in the treated eyes, while no such effect was found in the fellow untreated eyes. Following exposure to the respective antibiotics, coagulase-negative staphylococcal resistance to azithromycin increased from 58.6% to 95% ($p < 0.01$), that to ofloxacin

increased from 59.4% to 82% ($p = 0.02$), that to gatifloxacin increased from 19.7% to 42% ($p < 0.01$), and that to moxifloxacin increased from 25.6% to 65% ($p = 0.04$). While exposure to azithromycin resulted in an increased resistance to macrolides, it reduced that to fluoroquinolones. Lastly, all strains resistant to fourth-generation fluoroquinolones were also resistant to third-generation agents [43]. Contrary to the previous study, no difference in culture positivity rate or bacterial population was noted when comparing 40 eyes treated with 4-day topical antibiotics following monthly anti-VEGF injections to the fellow untreated eyes. In 11 patients treated with third- or fourth-generation fluoroquinolone drops, resistance to these antibiotics among their coagulase-negative conjunctival flora increased from 25% in the fellow untreated eyes to 87.5% in their treated eyes ($p = 0.04$). However, no change in resistance to trimethoprim was noted in the 29 patients treated with polymyxin-trimethoprim eye drops [44]. A retrospective study of 117,171 intravitreal injections performed at the Will Eye Hospital Retina Service between 2009 and 2012 revealed 44 (0.038%) cases diagnosed with endophthalmitis. Culture-positive results were obtained in 17 (39%) cases. There was no statistically significant difference in endophthalmitis incidence among the various intravitreal medications administered. The endophthalmitis rate was 0.032% (11 of 34,900) in patients who did not receive topical antibiotic prophylaxis and 0.049% (28 of 57,645) in patients who did. There was a concern that the use of topical antibiotics was associated with a trend toward increased incidence of both culture-negative endophthalmitis (odds ratio, 1.54; 95% confidence interval, 0.77–3.10) and culture-positive endophthalmitis (odds ratio, 1.51; 95% confidence interval, 0.47–4.83). However, using a simpler *Z*-score for two population proportions, there was a lack of significant difference between the two rates ($p = 0.22$). Culture yield was 36% whether patients received antibiotic drops or not. Visual acuity outcomes were significantly worse for culture-positive cases compared with culture-negative cases, regardless of antibiotic use [45]. In a Texas multicenter retrospective study, 30 cases of endophthalmitis (0.033%) were identified following 90,339 injections performed from 2011 to 2014. The use of prophylactic antibiotics once again appeared to increase the risk of endophthalmitis from 0.021% when avoided to 0.035% when used, although this was still not statistically significant ($p = 0.261$). The culture yield was 53% (16 of 30). The most common organisms isolated were coagulase-negative staphylococci in 62.5% of culture-positive patients, followed by *Streptococcus mitis* in 12.5% [46]. Contrary to prophylactic topical antibiotic use, repeated povidone-iodine 5% use did not promote emergence of antibiotic-resistant bacteria in conjunctival swab cultures performed on 13 patients undergoing monthly intravitreal injections [47].

Intravitreal injection guidelines were updated in 2014 to reflect the lack of evidence supporting the use of topical antibiotics to reduce the risk of endophthalmitis. The prophylactic measures recommended by this panel include [48]:

1. Surgical masks should be worn, or both the patient and the providers should minimize speaking during the injection preparation and procedure.
2. Povidone-iodine could be applied to the eyelashes and eyelid margins (optional).
3. Eyelids should be retracted away from the intended injection site for the duration of the procedure.

4. Povidone-iodine should be applied to the conjunctival surface, including the intended injection site, at least 30 s before injection. True povidone-iodine allergy is rare. Anaphylaxis has not been reported after ophthalmic application of povidone-iodine.
5. Postpone injection in presence of active external infection, including active blepharitis.

Interventional treatment for postinjection endophthalmitis is essentially the same as for post-cataract endophthalmitis, with the understanding that the microbial spectrum in postinjection endophthalmitis tends to be more virulent, leading to worse visual outcomes.

Endophthalmitis Following Trabeculectomy

Trabeculectomy has remained a mainstay of glaucoma filtering surgery over the past 30 years. In 2012 a total of 12,279 trabeculectomies was performed on Medicare-covered patients, with aqueous shunts (to an extraocular reservoir) increasing to 12,021 and mini-shunts to 5870 [49].

Trabeculectomy creates an aqueous bypass to the trabecular meshwork into a conjunctival bleb where it is absorbed. Bleb-related infections and inflammation could be divided into blebitis, when it is limited to the bleb with varying degrees of anterior chamber inflammation, and bleb-associated endophthalmitis, when this infection spreads posteriorly involving the vitreous gel.

Whereas most postoperative endophthalmitis arises in the days or weeks following penetrating surgery, bleb-associated endophthalmitis may also occur months or years later, when eye surface bacteria manage to cross the bleb conjunctiva because of its gradual thinning or outright defects. To study this rare complication adequately, a long post-trabeculectomy follow-up period is required, in addition to a large number of patients. An American insurance database review of 1461 patients who underwent trabeculectomies (or revisions) in 2007 and maintained insurance for the following 5 years found an incidence of 0.45% for bleb-associated endophthalmitis and 1.3% if other endophthalmitis diagnostic codes were included. The mean time of diagnosis of bleb-associated endophthalmitis after trabeculectomy was 45 months. This decreased to 33 months if the less specific diagnostic codes were included [50].

Microbiologic Spectrum of Bleb-Associated Endophthalmitis

While streptococci are more common in postinjection endophthalmitis than in post-cataract endophthalmitis, they are the most common organisms isolated in bleb-related endophthalmitis. A retrospective study of Wills Eye Hospital medical records from 1989 to 2001 identified 68 cases of bleb-associated endophthalmitis

(excluding cases of blebitis). Delay between glaucoma surgery and endophthalmitis ranged between 3 days and 9 years with a mean of 19 months, and 59% of vitreous samples were culture positive. Among those, 36% grew *Streptococcus*, 22% grew *Staphylococcus*, and 8% *Enterococcus*. No difference in visual outcomes was noted between the two species, but patients who were culture-positive fared worse than culture-negative cases, despite having better initial vision. Eyes treated initially with tap-inject progressed toward worse outcomes than those treated with initial vitrectomy, despite no significant difference in presenting vision between the two groups [51]. Another retrospective medical records study, from Bascom Palmer, identified 86 eyes that presented bleb-related endophthalmitis from 1996 to 2009. Sixty-three percent of cultures were positive. Among them, the most common organisms were 40% *Streptococcus*, 17% coagulase-negative *Staphylococcus*, 15% *Moraxella*, and 11% *Enterococcus*. Gram-positive bacteria accounted for 72% of organisms. Culture-negative eyes had better visual outcomes than culture-positive eyes despite similar presenting vision. Eyes with *Streptococcus* unsurprisingly fared worse than those with other gram-positive bacteria and those with coagulase-negative *Staphylococcus*, despite being treated more aggressively with vitrectomy rather than tap-inject. Among gram-negative bacteria, *Serratia*- and *Pseudomonas*-positive eyes had worse presenting and final vision [52]. Comparing data from Bascom Palmer on bleb-associated endophthalmitis between 1969 and 2008, there were significantly fewer *Streptococcus*-related infections during the 1996–2008 period relative to the 1969–1984 period. Similar to the trend observed in post-cataract endophthalmitis, *Streptococcus* prevalence may have decreased with more prevalent exposure to vaccination against *S. pneumoniae* species [53]. Why are *Streptococcus* the most common pathogen genus in bleb-associated endophthalmitis? Are they more likely to cross a thin conjunctiva? Are patients in the bleb cohorts older than those in the cataract cohorts? The risk of endophthalmitis indeed increases with age. For every 10-year increase in age, individuals were 16% more likely to develop endophthalmitis ($p < 0.001$) [8]. Isolation of bacteria on conjunctival swab cultures also increases with age, with culture-positive rates of 16.4% below age 60 increasing to 51.5% above age 81 ($p < 0.001$) [54]. The long-term use of benzalkonium chloride-containing glaucoma eye drops appears to decrease the culture-positive rate of conjunctival swabs in glaucoma patients compared to healthy controls. Counterintuitively, the share of isolates containing *Streptococcus* or *Staphylococcus aureus* decreases with use of benzalkonium chloride, while that of coagulase-negative *Staphylococcus* and gram-negative bacteria increases [55].

As mentioned previously, the preponderance of *Streptococcus* carries a dismal visual prognosis for bleb-associated endophthalmitis. Additionally, bleb-associated endophthalmitis affects eyes with a visual reserve already diminished by glaucoma. And there may be features related to the nature of bleb-associated endophthalmitis itself, which result in worse visual outcome. One may speculate that these features may include a difference in the inoculum-loading dose of pathogenic bacteria or a muted immune response compared with immediate postoperative incisional surgery endophthalmitis, or other host factors, which are yet to be identified. Treatment of bleb-associated endophthalmitis, while still based on the maxims elaborated by the

Table 6.7 Microbiological spectrum of post-trabeculectomy endophthalmitis

	Wills Eye 1981–2001 Busbee 2004 [51] Yield, 59%	Bascom Palmer 1996–2011 Jacobs 2011 [52] Yield, 63%	Bascom Palmer 1996–2008 Leng 2011 [53] Yield, 83%
Coagulase-neg staph	18.0%	17.0%	18.0%
S. aureus	4.0%	–	12.0%
Streptococcus sp.	36.0%	39.6%	30.0%
Enterococcus sp.	–	–	–
P. acnes	2.0	–	1.5%
P. aeruginosa	6.0%	5.7%	6.0%
Moraxella sp.	5.0%	15.1%	10.0%
Haemophilus sp.	4.0%	–	4.5%
Enterobacteriaceae		11.3%	7.5%
S. marcescens	4.0%	–	4.5%
Corynebacterium sp.	–	–	3.0%
C. albicans	2.0%	–	–

EVS, often involves more aggressive use of vitrectomy and multiple tap-inject procedures given the higher prevalence of virulent microorganisms. The microbiological spectrum of post-trabeculectomy endophthalmitis is shown in Table 6.7.

Conclusion

Endophthalmitis is a rare complication associated with any penetrating intraocular procedure. With an incidence usually remaining below 0.1% or 1 in a 1000, it can become more frequent during the early adoption period of new techniques and technology that involves wound construction, as proved to be the case with clear corneal phacoemulsification (0.247% or 1 in 405) or small-gauge vitrectomy (0.84% or 1 in 119). These spikes prove to be short-lived, however, with endophthalmitis rates returning to their baseline within 5 years.

The study of such a rare complication requires large datasets or number of patients, particularly if differences in rates of endophthalmitis are sought with a new procedure or treatment. Prospective trials, while the most valuable, would require standardization across many centers. Few, if any, have been completed besides the EVS 30 years ago and the ESCRS European multicenter study of postoperative endophthalmitis 10 years ago. Most of the studies on endophthalmitis are retrospective in nature. They are institution based or insurance carrier based. The institution-based studies are limited by incomplete follow-up of patients, who may consult different institutions for their surgery and complications. Most studies on microbiological spectrum could not, for instance, assess the incidence of the disease, as they could not accurately estimate the number of surgeries performed on the population (the denominator) referred for complications. Conversely, when an institution

reports a low incidence of endophthalmitis, one can question whether some patients have not sought care for endophthalmitis outside the care network where the initial surgery was performed. This fallible follow-up may partially explain why for postinjection endophthalmitis, rates reported by prospective clinical trials tended to be higher than those reported by retrospective studies [37].

Retrospective studies based on payors are limited by the coverage—for instance, Medicare in the United States covers mostly patients older than 65—and also by the lack of diagnostic code precision and clinical data available, such as visual acuity. These shortcomings of payor databases may be overcome by the development of "big data." The rise of electronic medical records has allowed the creation of massive databases and the mining of this expansive information stored in these records across institutions and payors. The American Academy of Ophthalmology initiated the Intelligent Research in Sight (IRIS) Registry in March 2014 as a longitudinal, clinical data registry to track patient outcomes over time and advance knowledge. The enrollment of IRIS has exceeded all expectations. As of November 2015, the registry included information on 61 million patient visits and 17.6 million unique patients. This registry allowed investigators to identify 400 cases of endophthalmitis within a year following cataract surgery performed in 2013 and 2014 on 511,182 patients and calculate an endophthalmitis rate of 0.06% per patient [10]. While the goal of such databases is to inform physicians of their outcomes, compare themselves with others, and improve their practice, the information can also be made available to payors who increasingly link physician reimbursement with performance. While linking financial incentives and disincentives to results collected from such "big data" registries may have a corrupting effect on the quality of the data in the long term, for the time being, they provide an important source of information on low-incidence diseases such as endophthalmitis.

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Part II
Specific Endophthalmitis

Chapter 7
Post-cataract Surgery Endophthalmitis

Subhadra Jalali

Cataract surgery has evolved, over centuries, into a very precise and one of the most successful surgeries on any human organ. An infectious process 'endophthalmitis' in this setting can pose one of the gravest risks to achieving a near-normal vision and in fact can lead to complete and irreversible loss of eye and vision.

Over the last few decades, the knowledge about the epidemiology, natural history, etiopathogenesis, causative organisms, diagnostic modalities, management, outcomes and prophylaxis of post-cataract surgery endophthalmitis has grown exponentially. We are hence currently better equipped to deal successfully with this grave situation. Post-cataract surgery endophthalmitis constitutes an overwhelming majority of all endophthalmitis worldwide. As a result, most of the information on endophthalmitis and the principles and practices contained in this book are also based on the knowledge and experiences from handling post-cataract surgery endophthalmitis; we will not repeat them here. These include the signs/symptoms, modes of presentation, microbiological profile, cluster outbreaks, prophylaxis, management options, randomised trials like the Endophthalmitis Vitrectomy Study (EVS) [1], etc. In this chapter we will highlight some important aspects that are unique to post-cataract surgery endophthalmitis and not covered elsewhere.

Epidemiology

Post-cataract surgery endophthalmitis has a variably reported incidence from nil to 1 in 200 cases [2, 3]. Depending on the technique of cataract surgery, prophylactic measures and the region reporting data, the rates have been steadily declining though in some cases introduction of some new step in surgery could increase the rates [4]. Current rates are estimated to be about 0.1% [5].

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Changing Trends

Cataract surgery evolution not only made it more precise and comfortable but also safer in terms of endophthalmitis. A major improvement was use of povidone-iodine and use of smaller self-sealing incisions. In a review of risk factors, the highest risks were noted in eyes that had clear corneal incisions, non-use of intracameral antibiotics (cefazoline or cefuroxime), posterior capsular break, intraoperative complications, silicone intraocular lens (IOL), and, to a lesser extent, the male gender and age more than 85 years [6]. Phacoemulsification seems to have lesser risks than extra- and intracapsular cataract surgery or manual small-incision cataract surgery [6–8]. Additional risk factors include ocular and systemic co-morbidities [9] or ambulatory surgery in lower socio-economic patients [10]. Most of these risk factors could be controlled by appropriate surgical techniques, preoperative evaluation, patient and staff education and surveillance. Clinical profile and signs and symptoms are given in detail elsewhere. Few important considerations specific to post-cataract surgery endophthalmitis are discussed.

Dilemma 1: One of the common clinical challenge is to differentiate infection from non-infection. Eyes with fulminant and frank infection are easy to diagnose and have a defined protocol of surgical intervention in all such cases. However, in some patients, especially in very early phase of an evolving infection, it is difficult to differentiate an infective from a non-infective inflammation (Fig. 7.1). The non-infective inflammations are at least ten times more common than infection following cataract surgery, but to mislabel an infection process as a non-infection condition could have disastrous consequences. So the clinical dilemma remains about how to manage eyes that look like non-infective endophthalmitis but we are unsure of definite infection [11].

Various approaches have been suggested. One approach, to be on the safer side, is to consider every postoperative 'unusual' inflammation as 'infective unless proven otherwise'. In such an approach, a prompt vitreous biopsy/tap or AC tap with intraocular antibiotics in all such cases should be considered. This approach

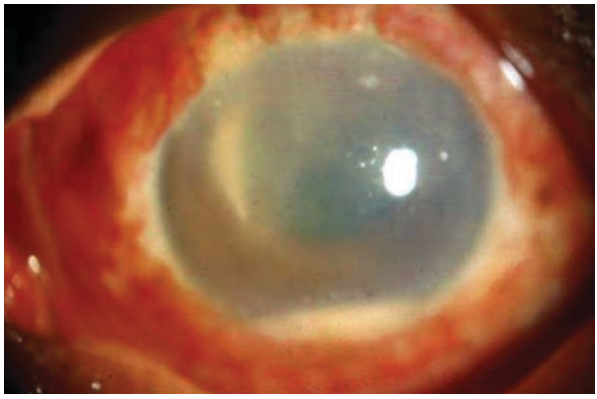

Fig. 7.1 Presumed non-infective endophthalmitis presented with corneal oedema, hypopyon and fibrin with normal ultrasonography and no adnexal inflammation. It needs close observation over the next 6–8 h with topical corticosteroids to look for early signs of resolution or worsening

will cover all of the low-grade and the evolving fulminant infections. The downside is that for every infective case that receives appropriate treatment, nine of ten cases that did not need this treatment would also receive unnecessary treatment and associated risks. Potential risks, though very rare, include drug toxicity, surgical complications like retinal detachment or globe perforation from anaesthesia, false laboratory positives, economic burden, physical and mental pain not only to the patient but also to family and the surgeons and an unnecessary load on the infrastructure of the operating room and the microbiological laboratory.

An alternate approach is to consider all such 'indeterminate' cases as inflammatory and 'presumed non-infective' [11]. This approach needs a detailed evaluation of the patient and an individualised approach based on a sound protocol of management. Detailed evaluation to reach a clinical judgement of 'presumed non-infection endophthalmitis' requires careful attention to the following factors, pre-, intra-, and postoperative:

1. Factors that could result in an inflammatory response need considerations. Detailed dialogue with the primary surgeon and patient along with a critical review of all previous documentation is needed to ascertain these factors:
   (a) Preoperative factors that could result in increased inflammation: Hypermature cataract; phacolytic and phacomorphic glaucoma; pseudoexfoliation; post-traumatic cataract; post-uveitis cataract; cataract in eyes with chronic angle closure on long-term medication, especially with pilocarpine; post-rubella cataracts in children; eyes with pre-existing undetected new vessels iris (NVI); eyes treated for neovascular glaucoma; and eyes with underlying retinal detachment.
   (b) Intraoperative factors that could result in increased inflammation: Poorly dilating pupils with or without posterior synechiae, floppy iris with frequent iris prolapse, retained viscoelastic, retained lens matter, prolonged surgical time, difficult lens removal, need for anterior vitrectomy, corneal pathology causing hazy view of lens, intraoperative increased bleeding including from globe perforation (peribulbar anaesthesia related)/angle vessels as in hypochromic cyclitis, pre-existing NVI, bleeding from surgical incision site or trauma to iris root, suprachoroidal/expulsive haemorrhage and uncooperative patient.
   (c) Postoperative factors that could result in increased inflammation: Poor compliance to medication, rebound inflammation on tapering topical steroids or anti-inflammatory eye drops, development of de novo NVI in eyes with underlying ocular ischemic syndrome due to increased metabolic demand on the hypoxic tissues and diabetes mellitus (possible, but not definitively proven).
2. Investigation: Ultrasonography is essential when the posterior segment view is not clear. Vitreous pin point echoes and membranes (Fig. 7.2, top) are suggestive of infective aetiology, but a normal ultrasonography does not rule out early infection. Isolated echoes could also occur in vitreous haemorrhage and cannot be

differentiated from echoes of infection in early stages. In old age, some vitreous debris gives vitreous echoes, and these could be differentiated from pathological echoes by careful comparison to the echoes in the non-infected fellow eye. Retained nucleus may be seen on ultrasonography (Fig. 7.2, bottom). Choroidal effusive detachment is more often seen in infective than non-infective cases. Pre-existing chronic retinal detachment could incite inflammation, but fresh choroidal and retinal detachment is more commonly seen in infective aetiology.

3. The next step is a meticulous evaluation of signs and symptoms and investigations: Symptoms that favour an infective aetiology are severe pain, nausea and vomiting usually a few hours after surgery. Fever and other constitutional symptoms could follow. Signs that favour an infective aetiology include adnexal oedema, diffuse mild stromal corneal oedema with minimal cellular infiltration (on slit lamp), inferior retinal exudates (Fig. 7.3), few or more areas of retinal vasculitis or retinal haemorrhages (Fig. 7.4) [12], raised or low intraocular pressure, wound leak including positive Siedel test and ultrasonography features (vide supra).

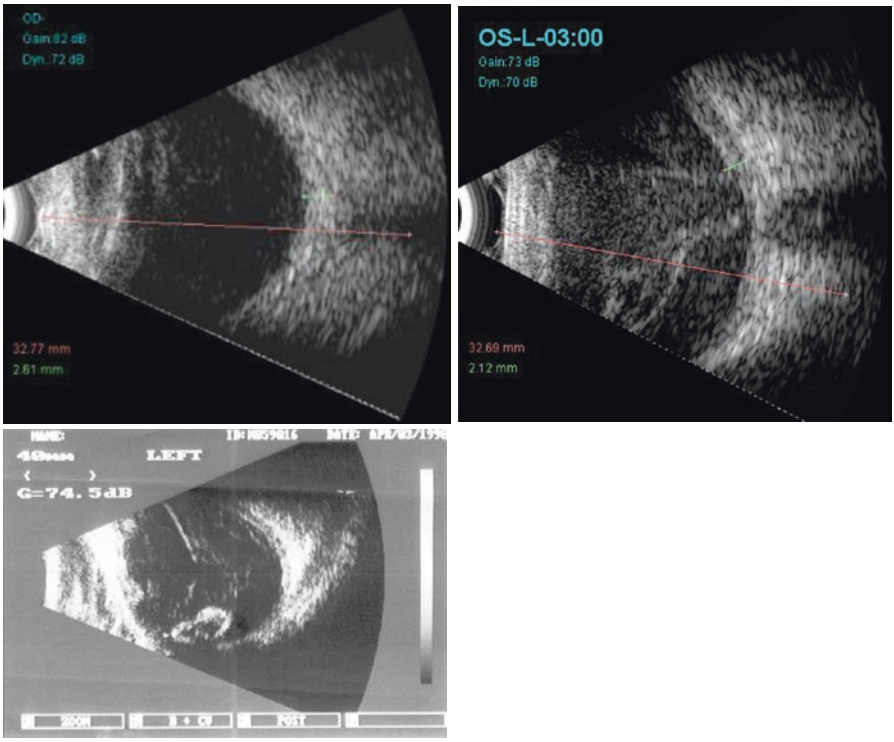

Fig. 7.2 Ultrasonography. *Top left*, moderately advanced endophthalmitis that shows fine dot-like echoes and normal choroidal thickening; *top right*, severely advanced endophthalmitis that shows membrane formation with dense echoes and choroidal thickening. *Bottom*—retained nuclear fragment with vitreous inflammation echoes causing an endophthalmitis-like appearance

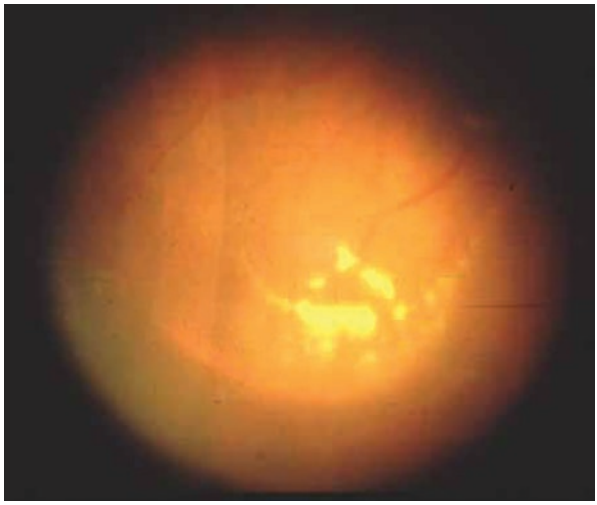

Fig. 7.3 Post-cataract surgery 1 week—visual acuity 20/25; cells in AC were suspected to having non-infective inflammation. Dilated fundus examination showed yellow exudates in the inferior retina suggestive of infection that could have been easily missed. Ultrasonography at this early stage was normal

Mild pain, reduced vision even to level of light perception only, clear cornea, minimal hypopyon, normal intraocular pressure and poor view of retina with pupil closed by a fibrin membrane or few anterior vitreous cells can occur both in infective and non-infective cases and are non-specific with substantial overlap in infection versus non-infection cases [13].

4. Once infection is not definitive and patient has 'presumed non-infective endophthalmitis', a definitive 'ten-point protocol'-based approach is followed [11]:
   (a) Document all the positive and negative findings, history and events as mentioned above.
   (b) Discuss situation with patient and family, and keep them ready for any possible change in plan for surgical intervention.
   (c) Start topical corticosteroids (prednisolone or betamethasone or dexamethasone) every half hour.
   (d) Attempt to dilate the miosed pupil rapidly. Use a combination of 5% phenylephrine and 1% tropicamide, one drop every 10 min for 4–5 doses. Use 2.5% phenylephrine and 1% tropicamide if patient is hypertensive. Use 2% cyclopentolate and 1% tropicamide if patient is allergic to phenylephrine. Do not use atropine at this stage because it is a poor mydriatic and onset of action/peak action is slow and acts only after a couple of days.
   (e) Use topical antibiotic, if desired, in routine dose of sixth hourly (options include tobramycin, moxifloxacin, ciprofloxacin, gentamicin, chloramphenicol) as per antibiotic policy of the treating centre.
   (f) Do not use systemic antibiotics. A single dose of intravenous or intramuscular dexamethasone can be given if non-infective status could be ascertained.

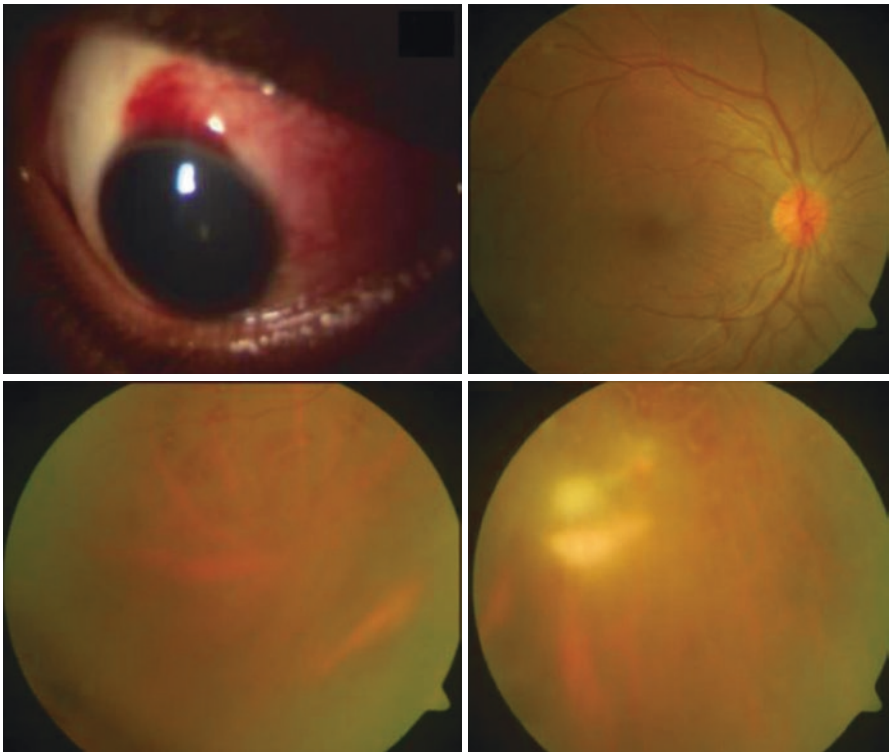

Fig. 7.4 Retinal vasculitis as the earliest sign of infection in post-traumatic infective endophthalmitis. Visual acuity was 20/25. Vitreous culture grew *S. epidermidis* [12]

(g) Admit the patient for above treatment, but do not delay the topical medications (as admission process takes its own time). If not admitting, keep the patient in the clinic area itself, and ensure topical instillation as per the protocol.
(h) Give antiglaucoma medication (oral acetazolamide, topical dorzolamide/timolol) as needed based on the intraocular pressure.
(i) Avoid or use only minimal oral or parenteral analgesic/anti-inflammatory drugs as they can camouflage the evolving pain severity, an important sign if it was not present earlier.
(j) Re-evaluate the patient in 4–6 h. This is the most critical step and has to be ensured. The symptoms and signs could be either same, worse or better. In each case a through and complete evaluation of patient is needed including detailed indirect ophthalmoscopy and slit-lamp retroillumination evaluation to look for presence and quality of the fundal red glow. Visual acuity and level of hypopyon are of less value in this evaluation. More important are retraction of fibrin and ability to dilate pupil well and get a peek into the posterior segment glow (Fig. 7.5).

At this stage one can decide to continue the same treatment and re-evaluate in the next 6 h or decide for surgical intervention. In our study, only 4 of 23

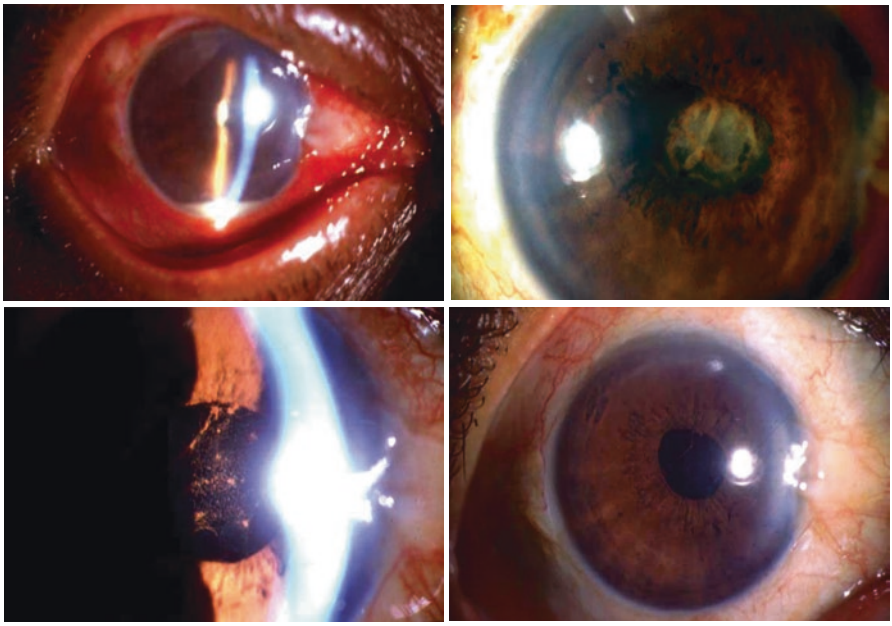

Fig. 7.5 Clinical course of presumed non-infective endophthalmitis with topical corticosteroids. *Top left*—at presentation, fibrin in pupillary area, miotic pupil and hypopyon with clear cornea. *Top right*—after 8 h of frequent corticosteroids and four doses every 15 min of phenylephrine and tropicamide, the synechiae are broken and fibrin is retracting. *Bottom left*—72 h later, fibrin is mostly resolved, and there was no hypopyon. *Bottom right*—complete resolution at 1 week

patients needed surgical intervention, and the remaining patients improved with medical therapy only. The patients who needed surgery often had low virulent and slow-growing organisms, and the delayed surgery still resulted in good outcomes [11].

Dilemma 2: Should an IOL be removed in a pseudophakic eye? The IOL is a prosthetic device implanted into the eye at the time of cataract removal or later as a secondary implant. General principles of infection in the presence of a prosthetic device in other parts of the body mandate that the implants be always removed for complete eradication of infection [14]. The reason is that most organisms form a biofilm around the prosthesis and these surfaces cannot mount a cellular or chemotactic attack against the microorganisms which tend to make the infection both chronic and recurrent. In the early 1980s, when the IOL usage became more widespread, IOL explantation along with vitrectomy and intraocular antibiotics was considered as the only way to eradicate completely post-IOL surgery endophthalmitis. However, over the next decade, vitreoretinal surgeons started to question this practice when it was not backed by any conclusive evidence. Based on experimental models [15] and after successfully eradicating acute bacterial infections in few cases where IOL was retained, more number of surgeons started to retain and not explant all IOLs [16, 17]. Currently, IOL explantation is a very rare practice and is limited to low-grade in-the-bag infections that are not eradicated by capsulotomy

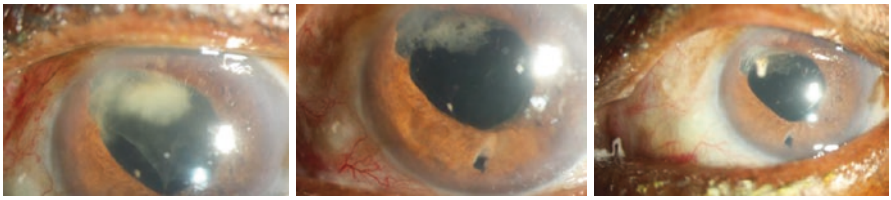

Fig. 7.6 Presentation and course of focal anterior fungal endophthalmitis after cataract surgery without vitreous involvement. *Left*: At presentation, yellow fluffy lesion localised to a small area, associated with fibrin in a relatively quiet eye with no hypopyon. *Middle*: 2 weeks after surgical excision of mass and intracapsular injection of amphotericin B and a surgical inferior iridectomy to relieve intercurrent papillary block. Oral itraconazole and topical natamycin resulted in near-complete resolution at 6 weeks, but a recurrence appeared behind IOL at 7 weeks while still on antifungals (*right*). IOL and capsular bag explantation with intraocular amphotericin B and oral itraconazole for 4 weeks eradicated the infection completely. Vitreous was uninvolved at all visits. Final visual acuity was 20/60

and in-the-bag antibiotics, fungal infections at primary or only at recurrence [18] (Fig. 7.6), very fulminant gram-negative endophthalmitis and rare cases of unusual fastidious organisms. In some cases of fulminant endophthalmitis, a thorough anterior chamber washing and removal of fibrin can avoid IOL explantation. The adhesion of organisms to the IOL surface and IOL haptic was studied and has shown that microorganisms (in this study it was *S. epidermidis*) adhere to all surfaces of IOL and that pretreatment with antibiotic (in this case vancomycin) helps reduce this adherence [19].

Dilemma 3: What is the ideal extent of vitrectomy—a complete vitrectomy or only a core vitrectomy or only vitreous biopsy and intraocular antibiotics (IOAB)? With the availability of small-gauge vitrectomy, it is being debated whether the EVS recommendations are done away with and vitrectomy is offered in all cases. There is no study on quality of vision and quality of life following the EVS strategy. EVS showed reasonably good outcomes when vitrectomy was not done, and only vitreous biopsy and IOAB were done in eyes with clear media and visual acuity of better than hand motion at 1 meter. Recent studies have put forth the view that a complete vitrectomy would provide better outcomes with minimal complications as all vitreous opacities are removed and recovery is faster [20]. Annoying vitreous opacities are almost always seen in eyes treated for endophthalmitis by vitreous biopsy only. Limited 'core vitrectomy' has been advocated in eyes with endophthalmitis due to risk of retinal tears and retinal detachment while inducing the posterior vitreous detachment with an underlying fragile and necrotic retina. Using current small-gauge and high-speed vitrectomy cutters, a near-complete vitrectomy is attempted by more and more surgeons in order to eradicate infection faster and reduce the chance of delayed retinal detachments. Extent of vitrectomy should be dictated by media clarity, and there should be no attempts at 'blind vitrectomy'. In very hazy media, the visibility of the disc and surrounding retina is considered adequate. During surgery, media clarity can be improved by various manoeuvres given in Table 7.1.

Table 7.1 Improving media clarity during vitrectomy for endophthalmitis

1. Anterior chamber washing
2. Removal of fibrin membrane over the IOL and pushing it into a corner of anterior chamber or removing it
3. Filling anterior chamber with clear viscoelastic (methylcellulose) during surgery and washing it out at the end of surgery
4. Corneal epithelium removal by blunt instrument without injury to Bowman's membrane
5. Posterior capsulotomy
6. Coating the posterior surface of intraocular lens with a thin layer of methylcellulose
7. Keeping the infusion fluid pressure at moderate levels
8. IOL explantation is only a last resort and often only in non-responding cases during subsequent surgeries. Rarely, it is done in primary surgery as a last measure in fulminant especially gram-negative cases

Dilemma 4: Management options in tunnel infections with or without associated frank endophthalmitis

A unique infection that can often progress to endophthalmitis specific to modern phacoemulsification and small-incision cataract surgery (SICS) is infection in the depth of the 'tunnel' self-sealing incisions. The infecting organisms get inoculated, usually at time of surgery or soon thereafter, into the depths of the wound, deep into the stroma of the sclera/cornea either at the main surgical incision site or at the 'side ports' or both. There may or may not be associated wound leak or endophthalmitis, but potential to progress to endophthalmitis is a distinct possibility. This deep 'tunnel' is out of reach of most topical, intraocular and systemic antimicrobials and is also too deep to yield the infective organisms by superficial corneal scrapings. This results in a chronic course, and the progression, slow or fulminant, depends on the virulence of the organism. In all cases, scrapings from depth of the 'tunnel after opening the lip of the surgical wound' are needed besides the anterior chamber wash and vitreous biopsy depending on extent of initial involvement. Causative organisms include virulent fungi like *Aspergillus* and bacteria including *Staphylococcus aureus* [21, 22].

Clinically, mild or more severe cellular and exudative infiltration and oedema are seen in the depth of the tunnel including the sclera or cornea or both, with varying amounts of tissue necrosis and with or without overlying epithelial defect. Anterior chamber involvement is seen varying from only few cells to mild fibrin, with or without hypopyon and dense exudates. Similarly, at presentation, there may be none, mild or severe vitreous involvement. Management approaches vary between two options: first, initial exhaustive medical therapy followed by surgical treatment only in progressive cases, and, second, surgical treatment earlier in course of disease especially in eyes with deep infection or scleral/corneal necrosis before it spreads to surrounding intraocular tissues (Figs. 7.7 and 7.8).

Eyes having tunnel infection, but with no obvious endophthalmitis at presentation, need daily detailed clinical evaluation for any progress to endophthalmitis while undergoing medical treatment. Retroillumination on the slit lamp is a good clinical technique in eyes with corneal haze to assess media status of the posterior segment (Fig. 7.9).

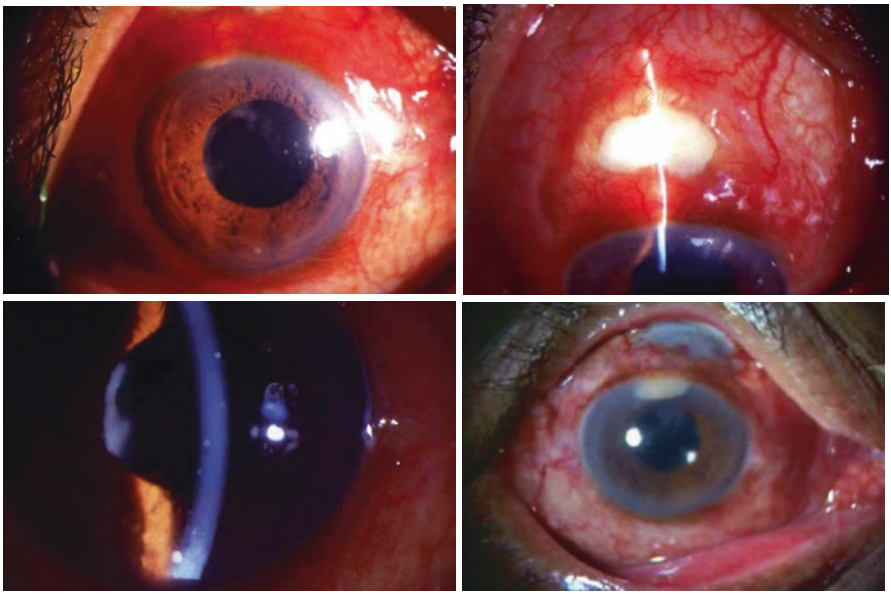

Fig. 7.7 Tunnel infection at early stage had severe scleral involvement (*top left*) and minimal corneal involvement (*top right*) with large keratic precipitates and no hypopyon (*bottom left*). Initially confused with surgically induced scleritis, it was found to be *Candida albicans* on scraping. After prolonged medical therapy, the scleral wound healed with thinning leaving behind persistent, loculated and slowly increasing deep corneal abscess. Bottom right image shows uninvolved anterior chamber and intraocular lens and capsular bag. (Courtesy: Prashant Garg, MD)

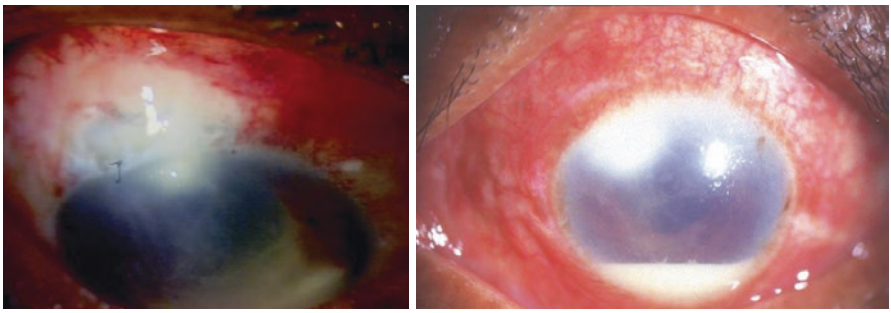

Fig. 7.8 *Left*: Tunnel infection with *Pseudomonas* species following phacoemulsification that resolved with medical therapy alone. *Right*: Filamentous fungal infection following clear corneal incision cataract surgery that was managed successfully with patch graft (Courtesy: Prashant Garg, MD)

Frequently Asked Questions

1. *If I suspect endophthalmitis, should I give an intravitreal injection before referring?*
   A: The key factor to a successful outcome especially in fulminant endophthalmitis depends on how quickly after onset of infection the eye receives intraocular

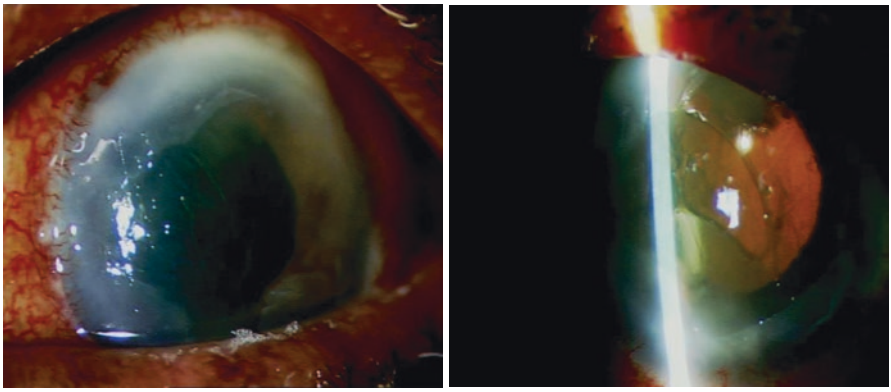

Fig. 7.9 Direct and retroillumination of post-cataract surgery tunnel infection without obvious endophthalmitis showing good fundal glow on retroillumination

Table 7.2 Factors that favour injecting antibiotic before referring

(a) Logistically patient will not reach the definitively treating doctor within 4–6 h
(b) Rapidly progressive or an evolving fulminant endophthalmitis
(c) Surgeon is skilled to give intraocular antibiotic
(d) Operating room infrastructure/personnel will not be available within 4–6 h to do surgery

antibiotic(s). The decision to inject an intravitreal antibiotic before referring the patient to a vitreoretinal surgeon has to be considered by the ophthalmologist who first examines the patient. Every ophthalmologist during residency must learn to prepare and inject intraocular antibiotics safely. Various factors to be considered are given in Table 7.2.

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Chapter 8
Blebitis and Bleb Related Endophthalmitis

Sirisha Senthil and Prashant Garg

Glaucoma is a chronic progressive optic neuropathy and is the leading cause of irreversible blindness worldwide [1]. The goal of glaucoma treatment is to control the intraocular pressure (IOP), which is most often achieved with antiglaucoma medications. When glaucoma is refractory to medical treatment, filtering surgery is performed. Described by Cairns in 1968 [2], trabeculectomy is considered the gold standard for glaucoma surgery. It is a partial-thickness guarded filtration procedure that allows aqueous to filter to the subconjunctival space forming a bleb, thereby decreasing the IOP. The conventional trabeculectomy has undergone various surgical modifications over half a century to improve the safety and efficacy of the procedure. Adjunctive antimetabolites have significantly improved the long-term survival of trabeculectomy, but at the expense of increased bleb-related complications [3, 4]. Infections after glaucoma-filtering surgery are infrequent but potentially devastating and mostly occur in the late postoperative period. Late leaking blebs and thin cystic blebs predispose these eyes to serious complications like blebitis and bleb-related endophthalmitis. Early identification and appropriate management is very crucial in salvaging these eyes and preventing loss of vision.

Epidemiology

The overall incidence of endophthalmitis after any intraocular surgery is reported to be 0.093% [5]. The incidence of endophthalmitis is much higher after glaucoma-filtering surgery [6] and is estimated to be 0.2–1.5% with non-augmented trabeculectomy [7–9] that increases with antimetabolite usage to 0.3–13.8% [3, 8, 10–13].

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Jampel et al. reported that risk ratio between the intraoperative use of antimetabolite agents and subsequent development of late-onset bleb-related infection (BRI) was around 2.48 with the use of mitomycin C (MMC) and 1.31 with 5-fluorouracil (5-FU) [11].

The incidence of early postoperative infection is estimated to be 0.12–0.19%, and the incidence of late-onset infections with partial-thickness filtering procedures is estimated to be 0.2–2.2% [10, 12–14] and that of blebitis is 0.08–0.55% [12, 15]. Surgical modifications like wide area application of MMC and suturing techniques have greatly improved the bleb morphology and have significantly reduced the incidence of bleb-related infections in the recent times from 5.2% (with longer duration and localized MMC application) to 1.2–1.3% (with shorter duration, wider area, and posterior subconjunctival MMC application) [15, 16].

Bleb-related infections can be localized involving only the bleb area called blebitis or could be associated with intraocular extension leading to bleb-related endophthalmitis (BRE). The progression of blebitis into endophthalmitis is probably a continuum of infection [6, 17, 18]. The prognosis of blebitis is usually good, unless infection has progressed to endophthalmitis. Despite prompt and intensive treatment of patients with bleb-related endophthalmitis, the outcomes remain unsatisfactory especially with virulent organisms and low initial visual acuity [19, 20].

Classification of Bleb-Related Infection by Greenfield and Katz [7, 10]

BRI is classified as:

Stage I: where bleb involvement is apparent.
Stage II: stage 1 + anterior chamber involvement, cells, flare, and hypopyon.
Stage III: stage II + vitreous involvement.
Stage III was further subdivided by Yamamoto [14, 21] into:
Stage IIIa: mild vitreous involvement
Stage IIIb: marked vitreous involvement

Blebitis: The term blebitis coined by Brown et al. in 1994 [21] describes a presumed infection in or around the filtering bleb, with surrounding congestion and mucopurulent infiltrate in the bleb. This may be associated with mild to moderate anterior chamber activity.

Bleb-related endophthalmitis: Bleb related endophthalmitis is more serious and is associated with hypopyon, vitreous involvement and severe visual loss. Bleb-related infections occurring within 1 month after the surgery are categorized as acute or early onset, and those developing later than 1 month are categorized as late onset [22].

It is important to differentiate between an early-onset infection from late-onset infection as they differ in terms of pathogenesis, causative agents, and prognosis.

Table 8.1 Risk factors for bleb-related infection [11, 23–25]

Association	Ocular	General
Strong	Thin and cystic bleb with late-onset bleb leak	
Midrange	Inferior or nasal bleb, intraoperative MMC usage, conjunctivitis, blepharitis, trabeculectomy alone compared to combined procedure, chronic antibiotic use, aphakia and pseudophakia, punctal plugs	Upper respiratory infection
Low-range	Juvenile glaucoma, nasolacrimal duct obstruction, releasable sutures, contact lens wear, bleb revision surgery: postoperative complications, history of prior bleb infection, high axial myopia	Young subjects, black race, presence of systemic diseases such as diabetes

Risk Factors for Bleb-related Infections

The eyes with a thin and cystic bleb with late-onset bleb leak are at increased risk of developing bleb-related infections [11, 23–25]. The odds of an eye with a bleb-related infection seen with a concomitant late-onset bleb leak is reportedly 25.8 times the odds of a noninfected eye having a late-onset bleb leak [24, 25].

Other risk factors are shown in the Table 8.1.

Yamamoto et al. described a significant association of aphakia or pseudophakia with the development of stage IIIa or stage IIIb bleb-related infection [14]. Thin cystic blebs are associated with intraoperative use of antimetabolites particularly MMC. The histopathology of these blebs shows very thin epithelium with breaks in the Bowman's membrane. The underlying stroma is relatively avascular and hypocellular. There is loss of goblet cells and absent mucin, which predisposes these blebs to infection either with the ocular commensals or with pathogens [26]. Peter DeBry et al. estimated that 5-year probability of developing bleb leaks was 18%, and bleb-related infection was 8% in patients when antimetabolites were used [3].

Microbiology

Causative organisms for blebitis: *Staphylococcus epidermidis* (more common) and *Staphylococcus aureus* are the commonest organisms to cause blebitis.

Causative organisms for bleb-related endophthalmitis (BRE): The most common causative organism associated with early-onset BRE is *Staphylococcus epidermidis* similar to that of acute endophthalmitis after cataract surgery. In contrast, the most common organisms causing late-onset endophthalmitis belong to *Streptococcus* species and *Haemophilus influenzae*.

Ramakrishnan et al. [27] reported early-onset blebitis (less than 36 months after trabeculectomy) to be associated with *Streptococcus* infection. These eyes had severe ocular surface disease and were associated with nasolacrimal duct obstruction.

The causative organism was coagulase-positive staphylococci in eyes with thin cystic bleb and blebitis; coagulase-negative staphylococci were associated with blebitis when there was associated bleb leak. *Corynebacterium* was isolated when blebitis was associated with blepharitis and *Streptococcus* was associated with releasable sutures [27]. Ohtomo et al. reported that BRE with highly pathogenic bacteria (*Streptococcus* species, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*) was associated with severe visual loss and carried poor prognosis even when intervened within 24 h [19].

Clinical Presentations

Typically the patients of blebitis and BRE report sudden onset of redness followed by pain in the eye, photophobia, discharge, and decreased vision. Many of these patients have prodromal symptoms like brow ache, headache, or external eye infections. The prodrome is longer in blebitis; it is accelerated in endophthalmitis with rapidly worsening ocular pain, reduced visual acuity, and redness within a few hours.

On clinical examination the area of the bleb is congested; there is loss of translucency of the bleb wall with milky content replacing the clear bleb and associated with mild to moderate anterior chamber reaction (Fig. 8.1a). Additionally, anterior chamber inflammation with hypopyon and vitritis may be noted in bleb-related endophthalmitis. (Fig. 8.2a). Ultrasound B-scan may be needed to evaluate the extent of posterior segment involvement.

Management: It is very important to examine these patients as soon as possible probably within an hour [20]. A thorough clinical examination including dilated fundus examination is mandatory to rule out endophthalmitis. One must also rule out blepharitis, nasolacrimal duct obstruction, and other risk factors. Workup must include conjunctival swabs under aseptic precautions, anterior chamber tap, and vitreous biopsy for microbiology investigation. Frequent instillation of appropriate antimicrobial therapy is the management of choice. Treatment could be with broad-spectrum antibiotics with activity preferably against gram-positive organisms. In addition to the spectrum of microorganism coverage, other considerations in choosing the most appropriate antibiotics include better kill kinetics and higher intraocular penetration of the topical antibiotics.

Fourth-generation fluoroquinolones such as moxifloxacin 0.5% or gatifloxacin 0.5% have broad-spectrum coverage and have better intraocular penetration and are widely used in the treatment of blebitis. In cases with severe blebitis, broad-spectrum fortified antibiotic combinations such as fortified cefazolin 5.0% and fortified gentamicin 1.4% are useful. At the initiation of treatment, the frequency of topical antibiotics should be every half to 1 h so as to attain adequate therapeutic concentration of the drug. To ensure close monitoring of compliance and response to therapy, admission and intensive medical care may be required. Subconjunctival injection of antibiotics or systemic therapy is not recommended unless the condition is severe and/or the compliance to topical therapy is

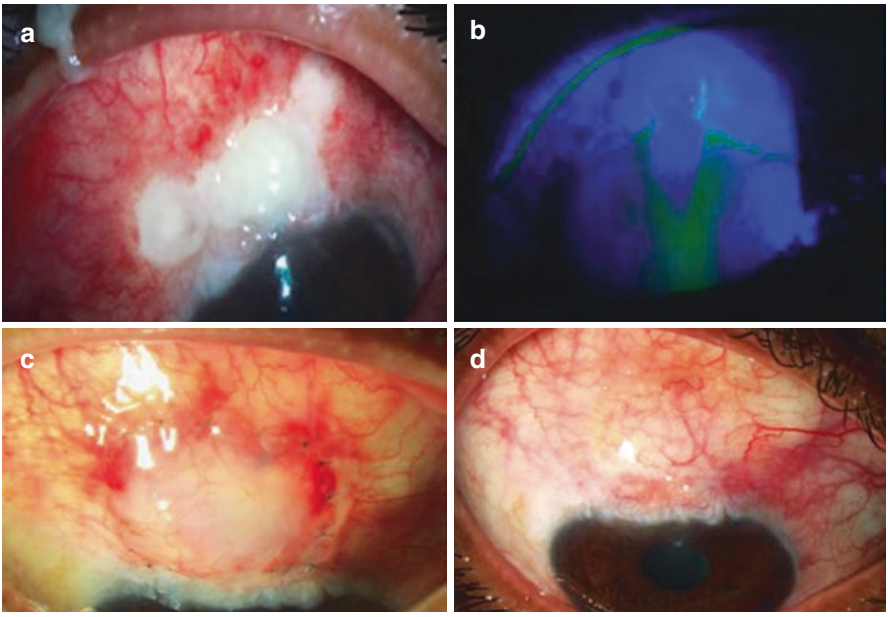

Fig. 8.1 Culture positive blebitis: A 27-year-old man presented with severe pain and redness with excess watering in his right eye for 2 days. He had mitomycin C augmented trabeculectomy for steroid-induced glaucoma 10 years ago. (**a**) The right eye showed severe superior conjunctival congestion; the bleb was avascular and necrotic, excess discharge with loss of bleb translucency suggestive of blebitis. Conjunctival swab showed gram-positive cocci; blebitis resolved in 3 weeks time with intense topical antibiotics (Moxifloxacin). *Staphylococcus aureus*, was grown in culture taken from conjunctival swabs and scrapings over the bleb area. The organism was sensitive to vancomycin, moxifloxacin, chloramphenicol, and cefuroxime. (**b**) Bleb leak was noted after resolution of blebitis. (**c**) The eye was treated surgically by conjunctival autograft harvested from the inferior conjunctiva. (**d**) Two months post-bleb repair, there was well-integrated conjunctival autograft with diffuse bleb; IOP was 10 mm Hg

questionable. Additional therapy includes topical cycloplegic agents and systemic analgesics. The intensive therapy should be continued for 48–72 h. Response to therapy could be measured by improvement in symptoms, reduction of congestion, and reduction in anterior chamber reaction. Once there is response to initial therapy, the frequency of antibiotic instillation can be reduced to two hourly administrations.

Once the blebitis resolves, the topical antibiotics should be stopped and never be tapered, and chronic use of antibiotics should be avoided, both of which could result in colonization of resistant microorganisms on the ocular surface. The empirical treatment should be initiated at the earliest and should not be delayed for microbiology workup and results. However, the subsequent microbiology results would guide in continuation of treatment or choosing alternative medications based on the sensitivity reports.

In the presence of AC involvement (stage II) or vitreous involvement (stage III), vitreoretinal surgeon's opinion and help with management would be required. It is

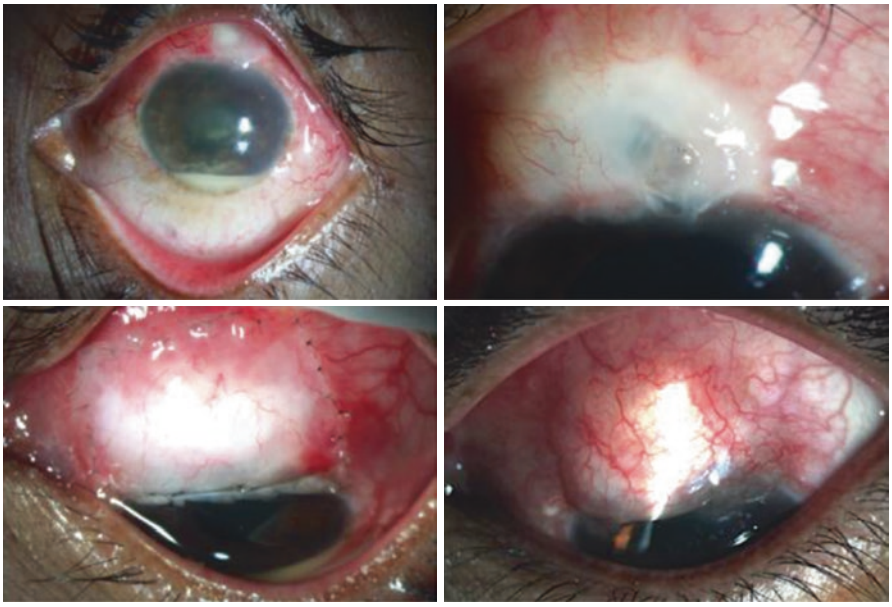

Fig. 8.2 Culture-negative bleb-related endophthalmitis. A 32-year-old man presented with severe pain and sudden decrease in vision for 1 day in his left eye, 3 years after trabeculectomy. *Top Left.* Blebitis with anterior chamber inflammation, hypopyon and few echoes in the anterior vitreous cavity on B-scan suggestive of endophthalmitis. He was treated with intensive topical and intravenous antibiotics, pars plana vitrectomy, and intraocular antibiotics. Both microscopy and culture were negative; hence, he was treated with broad-spectrum antibiotics covering gram-positive and gram-negative bacteria. *Top Right.* Endophthalmitis resolved and there was a thin cystic bleb, but no bleb leak. *Bottom Left.* Conjunctival autograft was performed 1 month after blebitis. *Bottom Right.* Two months later there was a well-healed autograft with diffuse bleb

prudent to begin intensive topical treatment similar to the treatment of blebitis before the referral.

One must remember that the management pearls of the Endophthalmitis Vitrectomy Study (EVS) for post-cataract surgery endophthalmitis cannot be applied to patients of endophthalmitis after glaucoma filtration surgery, more so in late-onset disease. A pars plana vitrectomy (PPV) and intravitreal antibiotic injection is more definitive treatment than a vitreous biopsy with intravitreal antibiotics. Studies have shown that more often poorer visual results (eyes with no light perception) are associated with the vitreous tap group compared to vitrectomy group [7, 28, 29]. Following vitrectomy one should continue treatment with frequent instillation of fortified antibiotic covering both gram- positive and gram-negative organisms till microbiology results are available. In addition, systemic antibiotics must be used. Topical and/or oral corticosteroids can be started after 24–48 h to decrease inflammation and scarring and to preserve the bleb function [7].

Once the infection is brought under control, one must reevaluate to identify the risk factors and treat them appropriately to prevent recurrent bleb infections [28]. Thin cystic blebs with late bleb leak need to be repaired. The technique of bleb

repair would depend on the site of leak and the health of the surrounding conjunctiva [29]. Both conjunctival advancement and conjunctival autograft have been successful in managing these thin cystic and leaky blebs [30, 31].

Summary

Blebitis and bleb-related endophthalmitis are serious and potentially vision threatening complications following glaucoma-filtering surgery. It is very important to diagnose the condition early and institute treatment at the earliest to salvage these eyes. All patients of glaucoma-filtering surgery must be clearly explained about the warning signals like brow ache, headache, associated light sensitivity, and decrease of vision. They should be asked to report to ophthalmologists immediately without any delay in appearance of these symptoms and signs. Early treatment carries better prognosis. Prognosis also depends on the type of organism and extent of intraocular involvement with blebitis and early-onset bleb-related endophthalmitis. Eyes infected with less virulent and/or less-resistant organisms enjoy better prognosis [28, 29, 32].

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Chapter 9
Traumatic Endophthalmitis

Tapas R. Padhi

Endophthalmitis following penetrating ocular trauma differs in many respects from other classes of endophthalmitis. Among patients with infectious endophthalmitis, posttraumatic endophthalmitis comprises approximately 25–30% of cases [1–4]. This is about ten times higher than postoperative endophthalmitis [5]. Risk factors of endophthalmitis following penetrating trauma include presence of an intraocular foreign body (IOFB) [1], lens rupture, delayed primary wound closure (>24 h), trauma or IOFB in a rural setting [1, 2, 6], trauma with contaminated objects and food stuffs [6, 7], and injuries by nails of pets and wild animals [1, 8]. Reports from India show that majority of traumatic endophthalmitis is seen in children and adolescence; injuries with bow-arrow, broom stick, and hypodermic needle are few of the peculiar mode of injury leading to traumatic endophthalmitis in this subcontinent [8–11]. Improperly disposed hypodermic syringes with needles are frequently used as toys by children to squirt water at each other with accidental globe penetration and endophthalmitis [12]. Hyphema and iris prolapse have been claimed to have some protective effect against endophthalmitis [13]. While hyphema is said to unlock the blood ocular barrier and release factors inhibiting bacterial growth, a prolapsed iris tissue could directly block the entrance of organisms inside the eye. Lacerations of length less than 2 mm have low chance of uveal prolapse (consequently no sealing of the wound by uveal tissue) and hence a higher risk of endophthalmitis than larger wounds [13].

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Etiology

A wide range of microbes that enter the eye following ocular trauma can cause infective endophthalmitis. The microorganisms are either derived from the normal periocular flora that gain entry after a delay in primary wound closure or carried into the wound by contaminated injury-causing objects. A variety of microbes have been implicated in the posttraumatic endophthalmitis including gram-positive cocci (most common), *Bacillus* species, fungi, and mixed infections [14, 15]. Although *Staphylococcus epidermidis* is the most common organism, as in postoperative acute endophthalmitis, other microorganisms are more frequently represented and the multi-microbial involvement is common. There is a high incidence of *Bacillus* species endophthalmitis following open-globe injuries, particularly in the setting of soil contamination. *Bacillus cereus* infection is associated with 2–7% of all penetrating wound to the eye [16]. The causative agents and their relative proportion vary depending on the geographical location, type of injury, living environment, and time from injury to wound repair. Posttraumatic endophthalmitis caused by a fungus is less common (range from 0% to 15.4%) than bacterial cases and are mainly found in open-globe injuries with vegetable matter or soil contamination with a chronic onset [2, 17, 18]. *Candida* is the most common fungus causing posttraumatic fungal endophthalmitis [19]. Sometimes there can be rare organisms due to some peculiar mode of ocular trauma like fishhook injuries during fishing in rural settings as shown in Fig. 9.1.

Clinical Feature

Symptoms and signs out of proportion to what is expected of a particular trauma or sudden worsening of symptoms should alert one of traumatic endophthalmitis [1]. Usually the initial symptoms are masked/modified by the damage induced by primary

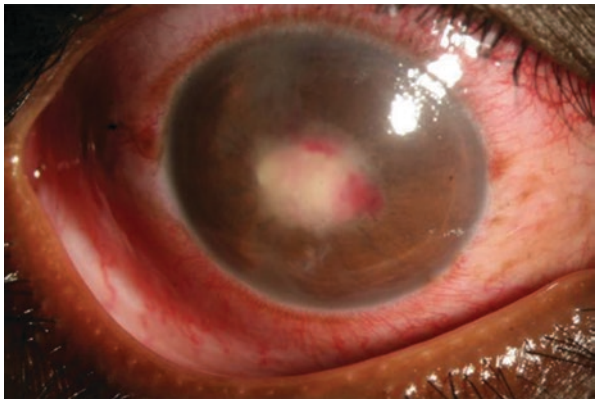

Fig. 9.1 Anterior segment picture of right eye of a case of posttraumatic chronic endophthalmitis following fishhook injury. Note a self-sealed sclera perforation temporally and blood tinged organized exudates in pupillary area

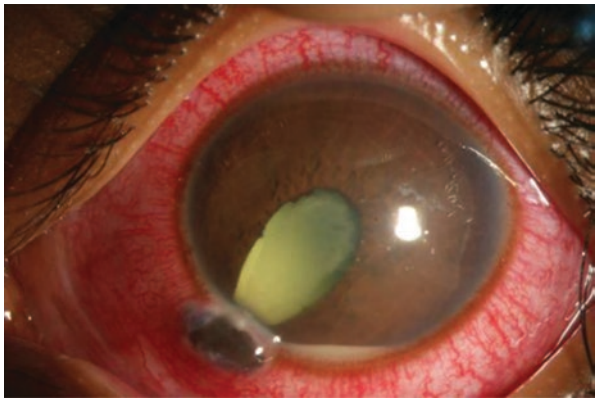

Fig. 9.2 Anterior segment picture of left eye showing scleral tear at inferonasal limbus with iris prolapse with hypopyon and dense yellow exudates in pupillary area

pathology causing a delay in the diagnosis and poor outcome. Sudden appearance of hypopyon (Fig. 9.2), increasing pain, retinitis, periphlebitis, vitreous haze, and vitreous echoes should alert one of endophthalmitis following trauma [1, 20].

Sometimes the symptoms can be delayed, and there is a mention of endophthalmitis diagnosed as long as 4–60 years following trauma [21]. The hypodermic needle-related injuries in children are particularly notorious for late/delayed presentation. Because of mild transient symptom at time of momentary pinpoint penetration by sharp needle tip, the initial impact is usually ignored by the child and presented few days to week later with severe symptoms. The site of penetration tends to be small and often occult and likely to be overlooked by the attending physician unless searched carefully under slit-lamp high magnification [12]. *Bacillus cereus* causes the most virulent and refractory form of endophthalmitis [22]. It is characterized by a rapid onset of severe pain and inflammation, hypopyon, chemosis, ring-shaped corneal infiltrate, progression to panophthalmitis, and irreversible destruction of the eye within hours to days. Reports mention a delay in treatment of over 6 h significantly reduces the potential for salvaging useful vision [15] because of permanent damage caused by tissue destructive exoenzymes [2, 22, 23]. Delayed onset, slowly progressive inflammation with minimal discomfort, and fluff or snow balls/string of pearl white inflammatory mass in the vitreous suggest fungal infection [24–26]. However, some of them can have pain and diffuse inflammation like bacterial endophthalmitis [17]; thus, it is prudent to investigate for fungus in addition to bacterial agents even with acute presentation.

Investigation

Often the media haze does not allow a detailed fundus evaluation and require a gentle B-scan (Fig. 9.3) under aseptic precautions to assess posterior segment. In case and whenever the globe integrity is severely affected, B-scan can be done in the postoperative period as soon as possible after primary repair.

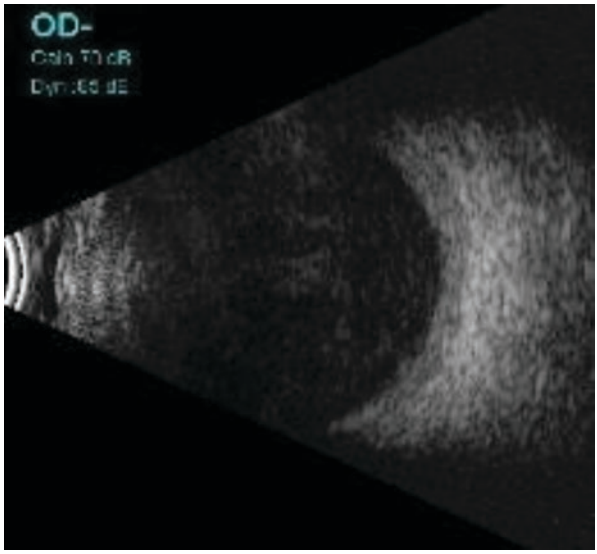

Fig. 9.3 B-scan of the left eye of a case of posttraumatic endophthalmitis showing multiple dot clump and membranous echoes in vitreous

Management

There is no general guideline for management of traumatic endophthalmitis unlike the Endophthalmitis Vitrectomy Study (EVS) recommendation for post-cataract surgery endophthalmitis. Prompt meticulous globe repair with systemic and broad-spectrum intravitreal antibiotics [27, 28] can go a long way in preventing endophthalmitis following acute penetrating injuries [8]. Injuries by needle, retained IOFB, lens rupture, smaller wound length, cases with exclusive corneal laceration, and deep injuries are associated with high risk of endophthalmitis and should urge for high vigilance [13]. Ability to filter out the clinical clues of infection among a variety of vague symptoms and signs of trauma play a crucial role in early detection of traumatic endophthalmitis.

Clinically suspected cases of traumatic endophthalmitis should undergo vitreous biopsy and vitrectomy along with empirical broad-spectrum systemic and intravitreal antibiotics (guided by the trauma history), sometimes in conjunction with the treatment for the primary intraocular trauma. Reports from South India show that vancomycin remains the drug of choice for empiric coverage of gram-positive organisms including *Bacillus* species, while ceftazidime is still the preferred choice for gram-negative organisms [29]. All cases of clinically diagnosed traumatic endophthalmitis might not have a positive culture in microbiology (culture independent). Similarly, the presence of a positive intraocular culture is not synonymous with endophthalmitis following penetrating trauma [1] and should be judged in the clinical context. Vitrectomy is often indicated for posttraumatic endophthalmitis with a goal to collect samples for microbiology; debulk vitreous toxins, microorganisms, and inflammatory debris; create space for the antibiotics to accumulate and spread; improve media clarity; and repair any underlying retinal pathology including foreign

body removal whenever required. As the inflamed retina could be fragile and is prone to tears, one should aim at safe vitrectomy. This can vary depending on the surgeon's expertise, available set up, and surgical feasibility with respect to coexisting collateral damage. Subsequent management depends upon the culture sensitivity report, clinical response, and complications if any. There is always a scope for an early second surgery once the infection is under control with a superior safety margin.

Endophthalmitis in the setting of a soil-contaminated foreign body has a higher likelihood of infection with *Bacillus*, *Clostridium*, and/or fungus and necessitates its prompt removal, if feasible. On the other hand, a metallic projectile penetrating the eye at a very high speed in a clean surrounding could be removed at ease if this cannot be removed safely during primary repair. A ruptured lens should preferably be removed during the primary procedure to avoid inflammation secondary to ruptured lens particles. Intravitreal and systemic steroid act as important adjunct to the primary treatment, take care of the inflammation, hasten recovery, and reduce collateral damage once the microorganisms start responding. However, they have to be used with extreme caution in cases of undetected/untreated fungal infection.

Microbiology

Like any other endophthalmitis, microbiology plays an important role in guiding subsequent treatment after initial management with broad-spectrum antibiotics. Unpredictable, atypical, and rare organisms are more common following penetrating trauma than that related to cataract surgery. One should be vigilant enough to look for additional organisms that might show up in culture plates after initial microbiology report. While a positive culture does not always mean endophthalmitis, a negative culture does not rule it out. Ariyasu et al. found that 33% of open-globe injuries were culture positive when aqueous was sampled. However, none of the patients progressed to develop endophthalmitis [30]. The prevalence of culture-negative cases of posttraumatic endophthalmitis has been reported to range from 17% to 42% [8]. Approximately 75% of all posttraumatic culture-positive endophthalmitis cases are caused by gram-positive organisms with *Bacillus* causing 20% of the infections [11]. Gram-positive bacilli in initial smear should be taken seriously and treated in the line of *Bacillus* spp. unless proven otherwise.

Prognostic Factors

Visual prognosis is affected by the virulence of the microbe, attendant inflammation, type of trauma, type and the extent of collateral ocular damage (e.g., retinal break or detachment), presence or absence of IOFB, timing and adequacy of the treatment, and finally immune status of the patient. Posttraumatic endophthalmitis

is typically associated with worse visual acuity outcomes compared with postoperative endophthalmitis [31] due to a variety of factors including associated comorbidities, more virulent organisms (*Bacillus cereus*) [32], and possible delayed diagnosis and initiation of treatment. Because of notoriously rapid progression, the interval between the onset of symptoms and initiation of treatment plays a crucial role in *Bacillus* endophthalmitis. A comprehensive review of posttraumatic cases of endophthalmitis caused by *B. cereus* reported that less than 30% of patients regained useful vision and that only 9% regained 20/70 vision or better [4]. Despite therapeutic and surgical intervention, 48% of *B. cereus* and other *Bacillus* species infections required evisceration or enucleation of the eye [4]. So early aggressive treatment is crucial for a better outcome [33].

Frequently Asked Questions

1. *What are the clues to suspect endophthalmitis in the setting of a penetrating trauma?*
   A: In the setting of a penetrating injury, following are the clinical clues that could hint at endophthalmitis:
   (a) Symptoms and signs disproportionately more than is expected of the type of underlying trauma.
   (b) Sudden worsening of symptoms/increasing pain after an otherwise normal recovery.
   (c) Purulent exudates at the site of injury.
   (d) Sudden appearance of hypopyon, corneal infiltrates, vitritis or vitreous opacification, vitreous infiltrate around foreign body, retinitis, or periphlebitis.
   (e) Slowly progressive inflammation in the absence of retained IOFB following primary repair could be indicative of fungal endophthalmitis especially in the setting of injury with vegetative matter.

2. *What are the risk factors for development of endophthalmitis in the setting of a penetrating injury?*
   A:
   (a) Retained IOFB
   (b) Setting of trauma suggestive of injury with contaminated weapon, contaminated foreign body (as with trauma in a rural setting), and organic objects
   (c) Open globe without sealing effect by uveal tissue
   (d) Delay in primary wound repair with wound contamination
   (e) Lens rupture

3. *Do prophylactic intravitreal antibiotics play a role in preventing endophthalmitis following open-globe injuries?*
   A: Controversies still continue. While reports from India mention the importance of systemic and intravitreal antibiotics in preventing endophthalmitis after

penetrating injury within 48 hrs, others suggest intravitreal antibiotics if ≥2 of the following risk factors are present:
(a) Delay in primary repair of ≥24 h
(b) Breach in the lens capsule
(c) Dirty wound [8]

4. *Do EVS guidelines of timing for vitrectomy apply for traumatic endophthalmitis?*
A: EVS was not designed for traumatic endophthalmitis; the conclusions can't be applied completely to endophthalmitis following trauma. While some recommend vitrectomy for all cases of traumatic endophthalmitis, others suggest vitrectomy in nonresponding cases or disease worsening despite initial vitreous tap and antibiotics. The decision depends on the treating surgeon and the clinical scenario. As a general rule, there is a greater tendency for early vitrectomy than in post-cataract surgery endophthalmitis.

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Chapter 10
Endogenous Endophthalmitis

Soumyava Basu

Endogenous endophthalmitis refers to the infection of the intraocular cavities that result from haematogenous dissemination of pathogens to the eye [1]. These pathogens typically reach the choroid or retina and then cross the blood retinal barrier to infect the vitreous cavity [2]. Unlike exogenous forms such as post-operative or post-traumatic endophthalmitis, the endogenous endophthalmitis is relatively rare and has been shown to account for 2–8% of all endophthalmitis cases in different studies [3, 4].

Causative Organisms

Endogenous endophthalmitis can be caused by a wide range of bacteria, gram-positive and gram-negative, and fungi, yeast and filamentous fungi. The microbiological spectrum is different from exogenous endophthalmitis, even for a given geographic region. In the Asian countries, bacteria, especially gram negative, are more common [5, 6], while in the Western populations, fungi are the predominant cause of endogenous endophthalmitis [3, 4]. This is in sharp contrast to exogenous endophthalmitis, which is commonly caused by gram-positive bacteria such as *Staphylococci* in the West and fungi, at least in some Asian populations, say in north India.

Risk Factors

Endogenous endophthalmitis can be associated with underlying systemic disease in up to 90% of cases [7]. These include diabetes mellitus, recent hospitalisation, sepsis, respiratory or urinary tract infection, intravenous drug abuse, indwelling catheters, various causes of immunosuppression such as malignancy, and acquired

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immunodeficiency syndrome (AIDS) [3–7]. The presence of infective foci/abscesses, elsewhere in the body, or surgical procedures, such as colonoscopy that can induce transient bacteraemia, are also important risk factors for endogenous endophthalmitis. There are reports of liver and lung abscess causing endogenous endophthalmitis with *Klebsiella* and *Aspergillus* infection [8]. However, a variable but significant proportion of patients may not have any obvious infective focus or risk factor for endogenous endophthalmitis. Such patients usually have a transient bacteremia from an occult systemic focus that needs a thorough investigation.

Clinical Features

Endogenous endophthalmitis can have a variable clinical presentation depending on the patient's systemic condition and virulence of the organism [1, 3, 4]. Most patients present with decrease in vision of sudden onset. Various symptoms and signs of anterior segment inflammation such as pain, photophobia, lid oedema, conjunctival and circumcorneal congestion, hypopyon and pupillary membranes may be present. It is important to examine carefully for signs of occult trauma, especially in children where the history may be unreliable. Anterior segment signs are more common in endogenous endophthalmitis with bacterial infection.

In general, endogenous endophthalmitis presents predominantly with posterior segment inflammation such as vitreous exudates, since the infection originates at the back of the eye (Fig. 10.1, top). *Aspergillus* may present with yellowish white subretinal lesions at the posterior pole, while *Candida* presents with white fluffy lesions projecting from the retina into the vitreous cavity (Fig. 10.1, bottom). Bacterial endogenous endophthalmitis is usually associated with greater vitreous inflammation and sometimes subretinal or choroidal abscess. Rarely, non-specific findings such as flame-shaped haemorrhages, Roth's spots and cotton wool spots may be seen. While some patients may present with obvious systemic disease, in other apparently healthy individuals, it is important to rule out recent fever, organ-specific infections and intravenous drug abuse.

Neonatal endophthalmitis is a special form of endogenous endophthalmitis seen in newborns with sepsis, very low birth weight and retinopathy of prematurity. It has two distinct clinical presentations [9]. Focal retinal infections generally have good visual prognosis, while fulminant nosocomial infections have poor outcomes. Clinical suspicion is crucial for early diagnosis, and vitreous aspiration and intravitreal antibiotic administration can be considered under topical anaesthesia, when general anaesthesia is contraindicated.

Diagnosis

Endogenous endophthalmitis is essentially a clinical diagnosis, based on the presence of characteristic ocular signs and often systemic risk factors. The diagnosis may be aided by B-scan ultrasonography that, besides showing vitreous exudates, may also reveal

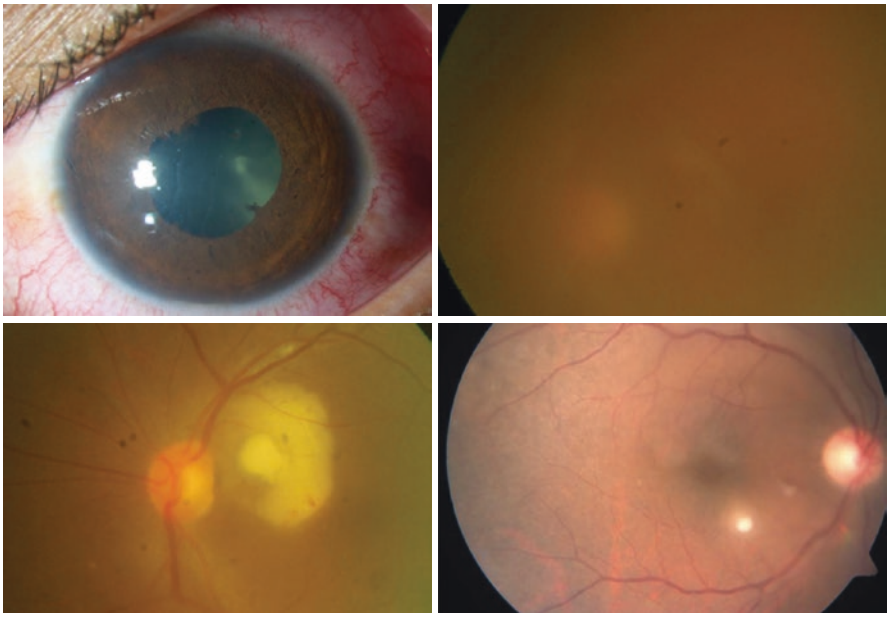

Fig. 10.1 Constellation signs of endogenous endophthalmitis. (*Top left*) Minimal anterior segment inflammation in a patient with dense vitreous exudates due to endogenous endophthalmitis; (*Top right*) dense vitritis with hazy view of the disc; (*Bottom left*) *Candida* endophthalmitis of the left eye, showing subretinal exudates with a preretinal projection into the vitreous cavity. (*Bottom right*) Another case of *Candida* endophthalmitis with a preretinal exudate but minimal subretinal involvement

choroidal abscesses that appear as dome-shaped choroidal lesions, underneath the vitreous exudates (Fig. 10.2, left). Rarely, optical coherence tomography may help delineate intra-retinal, subretinal or subretinal pigment epithelium location of infective foci.

The key test for confirmation of diagnosis is diagnostic vitrectomy. Since the infection originates at the back of the eye, sampling the vitreous near the infective focus greatly increases the diagnostic yield of the procedure. Rarely, subretinal biopsy of the subretinal exudates can help in identifying the causative organism (Fig. 10.2, right). Vitreous samples are subjected to standard microbiological examination (microscopy and culture) protocols for bacteria and fungi. Recently, quantitative real-time polymerase chain reaction (rt-PCR) has shown excellent sensitivity in diagnosis of bacterial and fungal infections, as compared to culture. Sugita et al. described a procedure that can be performed as quickly as 90 min [10]. Despite these advantages, current molecular techniques lack the ability to test for the entire range of antibiotic susceptibility and are prone to false-positive results, especially if care is not taken to prevent contamination of test samples.

Additional tests are required to rule out presence of systemic infection that may have been missed during clinical evaluation. The most effective method is blood culture using blood drawn on three consecutive days under sterile precautions. It is also useful to sample other extraocular sites of infection such as urine or pus from skin or other abscesses. A thorough internist evaluation can help in identifying occult infections (Table 10.1).

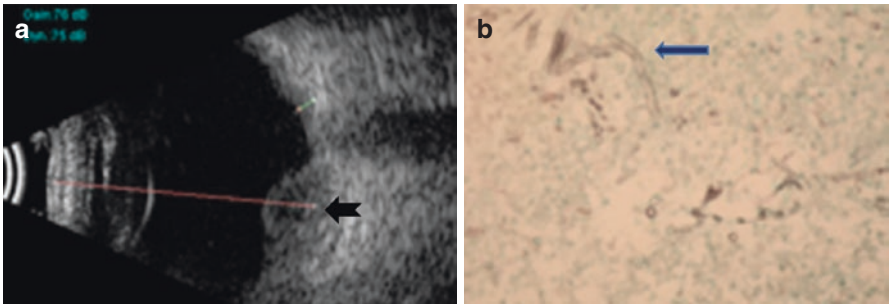

Fig. 10.2 A 41-year-old man presented with decreased vision in right eye, 1 day following percutaneous transluminal coronary angioplasty. The affected eye right eye had anterior chamber hypopyon with dense vitreous exudates. Ultrasound B-scan revealed dome-shaped elevation arising from the choroid (*notched arrow*, **a**) (*left*). Three consecutive vitreous biopsies did not grow any organism. However, a subretinal biopsy, 1 month after initial presentation, revealed presence of fungal filaments (*arrow*, **b**). (*Right*) The patient was treated with intravitreal and oral voriconazole, but vision could not be salvaged (Courtesy: Rajeev K. Reddy, MD)

Table 10.1 Etiological agents of bacterial and fungal endogenous endophthalmitis

Gram-positive bacteria	Gram-negative bacteria	Filamentous fungi	Yeast and yeast-like fungi	Other organisms
Streptococcus pneumonia	*Listeria monocytogenes*	*Aspergillus fumigatus*	*Candida albicans*	*Toxoplasma gondii*
α-Hemolytic streptococci	*Neisseria meningitidis*	*Aspergillus glaucus*	*Candida tropicalis*	*Toxocara canis*
β-Hemolytic streptococci (group A, B, G)	*Escherichia coli*	*Aspergillus terreus*	*Candida stellatoidea*	*Pneumocystis carinii*
Staphylococcus aureus	*Klebsiella pneumoniae*	*Fusarium* spp.	*Candida parapsilosis*	
Corynebacterium spp.	*Haemophilus influenzae*	*Sporotrichum* spp.	*Candida krusei*	
Cellulosimicrobium cellulans	*Serratia* spp.	*Coccidioides* spp.	*Cryptococcus* spp.	
Bacillus spp.	*Pseudomonas aeruginosa*	*Mucor* spp.	*Torulopsis* spp.	
Clostridium spp.				
Nocardia asteroids				
Mycobacterium tuberculosis				
Actinomyces spp.				

Differential Diagnosis

The diagnosis of endogenous endophthalmitis could be tricky, particularly in individuals who do not have obvious systemic risk factors. It is important to rule out different forms of endogenous uveitis that present with dense vitreous

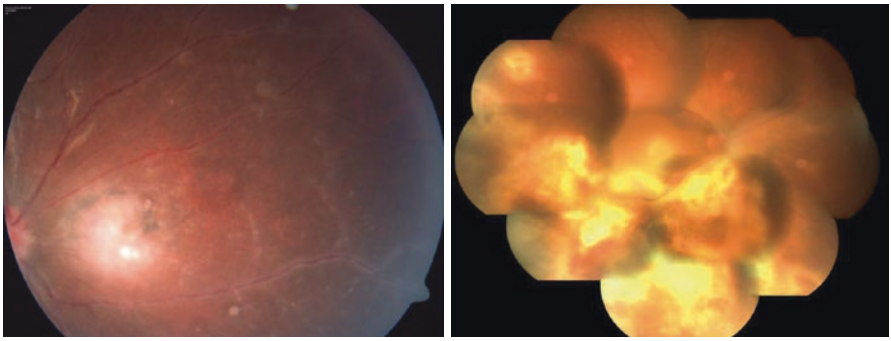

Fig. 10.3 (*Left*) Ocular toxoplasmosis. Colour fundus photograph of the nasal quadrants of right eye showing a focus of active retinitis, associated with pigmented scars, suggestive of recurrent ocular toxoplasmosis. It is crucial to identify such clinical patterns through the vitreous haze, to make an accurate etiologic diagnosis and initiate appropriate antibiotic therapy. (*Right*) Acute retinal necrosis. Colour fundus photograph of the right eye showing large areas of confluent necrosis in inferior fundus, extending from the periphery to the posterior pole and associated with mild vitritis and areas of scarring. In eyes, with dense vitreous reaction, and smaller areas of necrosis, the diagnosis may be missed at initial examination

inflammation. Most important are two common causes of infectious retinitis—acute retinal necrosis and ocular toxoplasmosis. It is useful to look through the vitreous exudates for bright retinitis lesions at the posterior pole (toxoplasmosis, in association with pigmented scar; Fig. 10.3, left) or at the periphery (acute retinal necrosis; Fig. 10.3, right). Tell-tale signs of active or healed retinitis in the other eye may also help in confirming the diagnosis. Rarely, a patient with a first episode of HLA-B27-associated uveitis, presenting with anterior chamber hypopyon and significant vitreous reaction, may also be mistaken for endogenous endophthalmitis. This may be differentiated by systemic history and identifying predominantly anterior segment inflammation.

Treatment

Treatment of endogenous endophthalmitis depends on the severity of ocular inflammation, including media clarity, presence of systemic risk factors and identification of causative organism.

Local Therapy

Although vitreous samples can be obtained by aspiration, it is advisable to perform a ‘more-than-core’ pars plana vitrectomy in these patients, if the patient can tolerate surgery, and adequate visualisation of the posterior segment is possible [11, 12]. This procedure not only helps in retrieving adequate sample for microbiological

evaluation but also significantly reduces the infectious load within the vitreous cavity. In eyes where a focal lesion (intra- or subretinal or choroidal abscess) is visible during initial evaluation, it is useful to begin sampling near the lesion under direct visualisation, to obtain greater diagnostic yield. This is followed by empirical intravitreal antibiotic therapy, usually vancomycin and ceftazidime/amikacin, in standard doses to cover both gram-positive and gram-negative organisms, respectively. The decision for repeat injections depends on response to initial treatment and microbiological results.

For fungal endogenous endophthalmitis, suspected on basis of clinical signs described earlier, or diagnosed after microbiological evaluation, intravitreal voriconazole or amphotericin B, can cover both yeast and filamentous fungi, though amphotericin B has a poorer intraocular safety profile.

Systemic Therapy

Since endogenous endophthalmitis results from haematogenous dissemination of pathogens to the eye, systemic antibiotic therapy to treat the underlying source of bacteraemia/fungemia is a vital adjunct to local treatment. However, it should be initiated after a series of blood cultures have been obtained. Fluoroquinolones are typically used for broad-spectrum anti-bacterial therapy unless antibiotic sensitivity reports show resistance in isolated organisms. Fluconazole, 400–800 mg daily for a minimum duration of 6 weeks, is recommended for *Candida* infection, while intravenous Amphotericin B is most useful for *Aspergillus* infection. The role of corticosteroids, systemic or intraocular, remains controversial in management of endogenous endophthalmitis.

Prognosis

The overall visual and anatomical prognosis of endogenous endophthalmitis is generally unfavourable compared to exogenous endophthalmitis. Important prognostic factors include timing of diagnosis and treatment, presentation of visual acuity, virulence of organisms, location of infective foci at the posterior pole and presence of underlying systemic disease such as diabetes mellitus. Early diagnosis and treatment is crucial particularly when systemic clues are absent. *Aspergillus* and other filamentous fungi and methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacteria such as *Klebsiella* are known to have worse prognosis.

Conclusions

Successful management of endogenous endophthalmitis depends on prompt diagnosis and treatment. The key is to identify the causative organism and its systemic focus and any underlying risk factors. Early pars plana vitrectomy can significantly improve the chances of favourable treatment outcomes.

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Chapter 11
Fungal Endophthalmitis

Umesh C. Behera

Fungal endophthalmitis is relatively uncommon but potentially devastating both in terms of visual and structural outcome. Quite similar to bacterial endophthalmitis, fungus are inoculated directly from environmental sources by trauma or intraocular surgery in exogenous fungal endophthalmitis and as hematogenous spread following systemic fungal infection in endogenous fungal endophthalmitis.

The endogenous endophthalmitis is discussed in detail in another section. Hence, this chapter would focus on exogenous fungal endophthalmitis and its management. Unlike endogenous fungal endophthalmitis that occurs in immunocompromised states and in patients with systemic debilitating disease, exogenous fungal endophthalmitis occurs in immune-competent or immune-suppressed patients. Fungal microbes are directly inoculated into ocular tissue either by injury with vegetable/organic matter or by intraocular surgeries like cataract extraction and corneal transplant [1–2]. It may be associated with cluster infections as have been reported by used contaminated intraocular lenses [3], contaminated irrigating solutions [4], ventilation system repairs [5] and hospital construction activities [6]. The disease is reported more commonly in tropical regions, and the incidence of traumatic and postoperative fungal endophthalmitis do not differ widely [7]. The incidence after cataract extraction could be as high as 21.8% of all culture-positive cases of endophthalmitis as reported from India [8]. The incidence inclusive of traumatic and endogenous endophthalmitis account for 4.1% of all culture-positive infections [7].

Clinical Pointers to Fungal Endophthalmitis

The characteristic clinical signs with which fungal endophthalmitis may present are listed in Table 11.1 and shown in Figs. 11.1 and 11.2.

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Table 11.1 Clinical features of fungal endophthalmitis

Anterior segment	Posterior segment
Lid edema Intense conjunctival congestion Dry appearing hypopyon Yellowish white nodular exudates on the iris and lens surface Yellowish white infiltrates at corneo-scleral wound	Intense vitritis Vitreous membranes String of pearl like arrangement of vitreous exudates Creamy white well circumscribed chorioretinal lesions

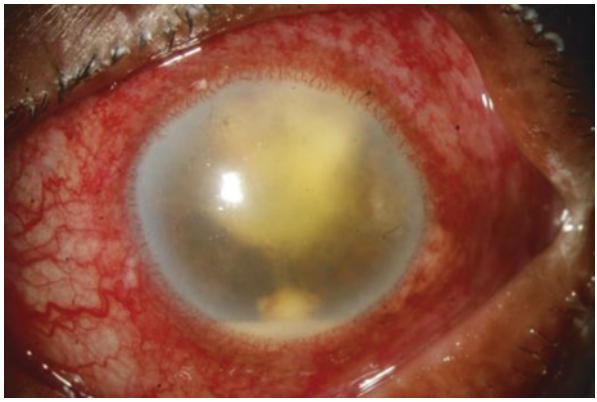


Fig. 11.1 Intense conjunctival congestion, chemosis, corneal edema, fluffy exudates at pupil streaming from the cataract surgery wound, nodular and organised hypopyon seen 2 weeks after cataract surgery. Growth of *Candida* was significant on vitreous and aqueous sample culture

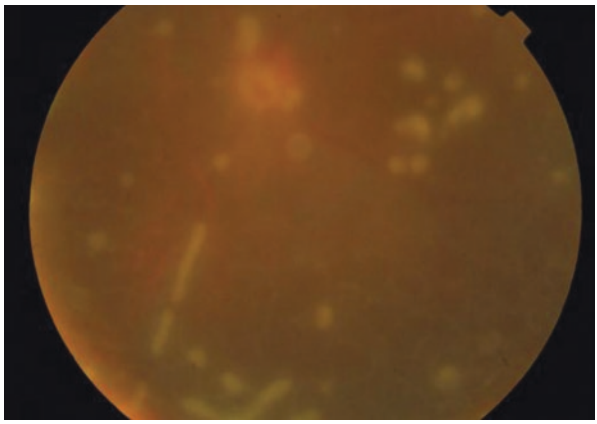


Fig. 11.2 Characteristic creamy white vitreous exudates of fungal endophthalmitis seen populating the inferior fundus in a stringlike arrangement within a hazy media because of intense vitritis in a cataract extracted eye

The time interval from surgery to infection in postoperative endophthalmitis may range from as low as 48 h to as long as 7 months [9]. The presenting vision in both postoperative and traumatic endophthalmitis is invariably low, >20/400 in only 5.7–11.1% of postoperative patients, and HM to CF (hand motion to count finger) in almost all cases of traumatic fungal endophthalmitis [7, 9]. It is often difficult to differentiate fungal endophthalmitis from bacterial endophthalmitis on clinical grounds; hence, most of the reported case series on fungal endophthalmitis had treated the eye condition empirically as bacterial endophthalmitis until the microbiological results were available.

Common Fungal Associations

Any saprophytic fungi found in natural habitats may cause exogenous fungal endophthalmitis. It is associated with a variety of species: common pathogens include *Aspergillus* species and *Candida* species (predominantly in postoperative cases) [7–10] and *Fusarium* species (predominantly following trauma and keratitis) [11]. The other mycotic agents include *Paecilomyces* species and *Acremonium* species [12]. One of the large case series from north India [7] reported *Aspergillus* species as the most common (54.4%) isolated fungus, followed by yeasts (24.6%) and melanised fungi (10.5%).

Laboratory Diagnosis: Microbiological

Direct microscopy of the ocular specimen is the most commonly followed method of identifying fungal pathogens as it is rapid and cost effective. Microscopic examination under 10% potassium hydroxide (KOH) preparations can identify the fungal structure and the distinctive morphology. KOH dissolves the human tissue and allows visualisation of the alkali -resistant fungal structures. Special stains like calcofluor white and Fontana-Masson stain are used to stain the cell wall and presence of melanin in the smear, respectively. Nevertheless, a direct microscopy is less sensitive than culture, and a negative smear does not rule out fungal infection [13].

When cultured, at least two different media are chosen for pathogen identification—selective (Sabouraud agar) and non-selective (chocolate, blood agar and brain heart infusion broth). They are incubated in room temperature as the growth is optimum between 25 and 37°C. The specimen is incubated for at least 4 weeks before reporting it negative. The yeasts and the moulds are distinguished from each other under direct microscopy. The main characteristics of commonly isolated fungal species are described in Table 11.2 and illustrated in Fig. 11.3.

Molecular Laboratory Diagnosis

Polymerase chain reaction (PCR) is invaluable in the diagnosis of fungal endophthalmitis. It has a high degree of specificity and sensitivity, reduces laboratory diagnosis time and is particularly useful in those cases where cultures have not yielded any growth. The routine use of PCR for the detection of fungal DNA, using pan-fungal primers ITS1 and ITS4 for the diagnosis of fungal pathogens on specimens as an adjunct to conventional microscopy and culture, is likely to increase diagnostic yield [15–17]. In one of the traumatic endophthalmitis studies PCR identified the organism in all the specimens when the cultures were all negative [18].

Table 11.2 Characteristics of commonly isolated fungal species (adapted from [14])

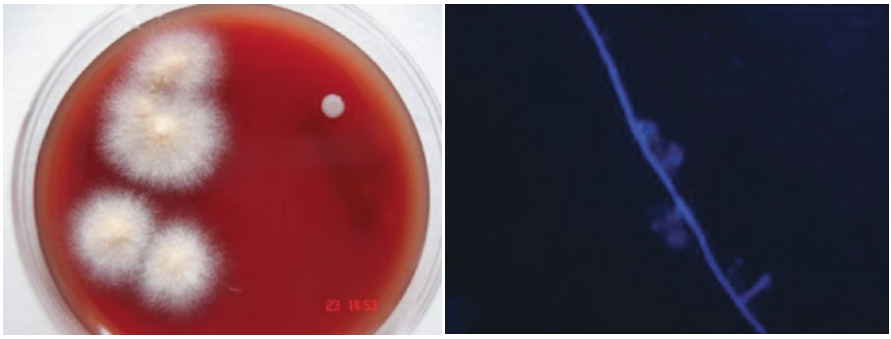
Fungus	Miscroscopic features in clinical specimen	Macroscopic features in culture	Microscopic features in culture	Additional tests for identification
Candida	Oval budding yeasts 2–10 μm in diameter; pseudohyphae may be present	Yeast colonies are pasty, creamy, white, and opaque	Blastoconidia, pesudohyphae, chlamydospore in some species	Carbohydrate assimilation Morphology on corn meal agar
Aspergillus	Septate, dichotomously (45°) branched hyphae of uniform width (3–6 μm)	Mould colonies are bluegreen, yellowgreen, or black and velvety, cottony	Hyphae are hyaline and septate, but microscopy varies with species	Identification is based on microscopic evaluation of the colony
Fusarium	Hyaline, septate, dichotomously branching hyphae Angioinvasion is common. May be indistinguishable from *Aspergillus* spp.	Colonies are purple, lavander, or rose-red with rare yellow variants	Both macro- and microconidia may be present Macroconidia are multicelled and sickle or boat shaped	Identification is based on microscopic and colonial morphology. DNA sequence-based identification is increasingly important

Management

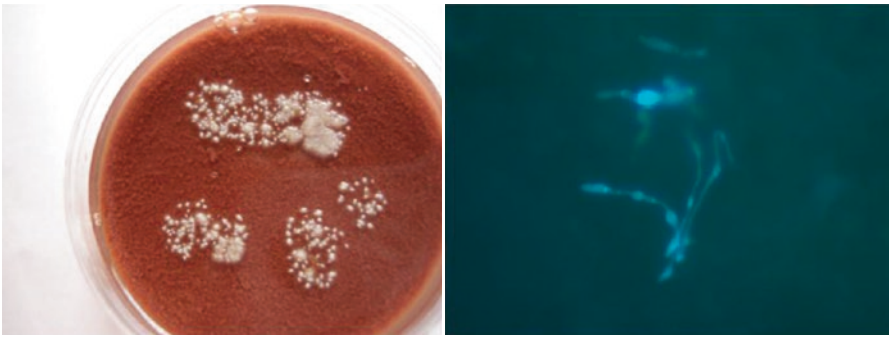
Treatment of fungal endophthalmitis has unique challenges, principally because of the following reasons: the diagnosis is often challenging, the choices of available therapies are limited, and the outcomes are frequently unfavourable. As the disease incidence is low and because there is no randomised control trial, the treatment protocol is still not optimised.

The management of the condition begins with collection of aqueous and vitreous sample for pathogen identification. Because of better recovery of fungi, the vitreous sample is considered more valuable than an aqueous tap [19]. An ultrasonography of the vitreous is mandatory to assess the vitreous involvement and associated ocular tissue damage. A standard two-/three-port vitrectomy at high cut rate and low vacuum for biopsy is considered safe. Presence of choroidal or retinal detachment should not deter a surgeon to sample the vitreous. A meticulous clearing of anterior segment exudates through a corneal paracentesis may improve visualisation of the anterior vitreous to allow direct view of the vitreous cutter at the anterior vitreous face. In rare instances when anterior vitreous face cannot be viewed due to poor corneal clarity, one may restrict to an aqueous tap alone, which can be done by aspirating anterior chamber fluid transcorneally by a 26G hypodermic needle mounted on a tuberculin syringe. Approximately 0.2–0.3 ml of vitreous sample or

Aspergillus



Fusarium



Candida

Fig. 11.3 Composite image of the growth of fungal agents on solid media and the corresponding photomictographs of the hyphae and spores stained with 10% KOH and 1% calcofluor white. *Top*, Aspergillus; *middle*, Fusarium; *bottom*, Candida

0.2 ml of aqueous sample is collected for microbiological culture and microscopy. Depending on the proximity of the microbiology laboratory, the sample may either be sent in a sterile closed box or may be directly plated in the operating room. In addition to the culture, wet mount preparations of the sample with 10% KOH help

identify fungal hyphae. The sensitivity of the test is higher when calcofluor white is added to KOH and the specimen is observed under fluorescent microscope [13].

Achieving adequate concentrations of antifungal antibiotic in the infected tissues is crucial to treatment success. The choroid and retina are highly vascular compared to the vitreous, and the vascular compartments are separated from intraocular structures by the blood-ocular barrier. Thus, infection localised to the chorioretinal layers, which are not protected by this barrier, can be treated with systemic antifungal agents, but treatment of other intraocular infections requires penetration of the antifungal agent through this relatively impermeable barrier.

Before the availability of newer triazoles, the most common antifungal treatment for fungal endophthalmitis was intravenous and/or intravitreal amphotericin B. It is effective against a wide range of fungal pathogens, but its utility in treating fungal endophthalmitis is limited by poor ocular penetration and the potential intraocular toxicity such as intense intraocular inflammation, retinal necrosis, and cataract formation [20, 21]. It would cause chills, fever, nausea, vomiting, diarrhoea, dyspnea, malaise, anaemia, arrhythmia, hypokalemia, hearing loss and renal failure when administered systemically [22].

With the availability of newer triazoles such as fluconazole, itraconazole, voriconazole, posaconazole and ravuconazole, the choice of treatment has moved away from the traditional use of amphotericin B. These newer drugs are less toxic and have a better bioavailability in vitreous when administered orally [23]. Fluconazole, an older-generation triazole, has been used systemically as a supplement or alternative to amphotericin B, but it lacks the broad spectrum of coverage necessary for the most commonly encountered fungal infections in the eye. Furthermore, intraocular penetration is marginal. Itraconazole is rarely used in the treatment of ocular fungal eye infections, as it lacks a broad spectrum of coverage, specifically against *Fusarium* species [24].

Voriconazole is the most preferred among the azoles currently in use for treatment of fungal endophthalmitis. It is a second-generation azole derived from fluconazole and can be administered intravitreally, orally and intravenously. It is effective against most *Candida* species, *Aspergillus* and *Cryptococcus* [25]. It has excellent intravitreal penetration after systemic administration, and the toxicities include visual disturbances like photophobia and elevation of hepatic enzymes [26].

After the large outbreak of *Fusarium* keratitis in contact lens wearers in 2005, interest in voriconazole to treat fungal eye infections increased among ophthalmologists, who realised the benefits of this broad-spectrum triazole agent in treating the difficult problem. Many studies on the distribution of voriconazole within ocular compartments were performed during treatment of complicated *Fusarium* keratitis. Most studies on voriconazole are from humans. The rationale for injection of voriconazole lies in its better safety profile than amphotericin B and its ability to achieve high levels of drug concentration in the vitreous. The details of common antifungals used in treatment of endophthalmitis are listed in Table 11.3.

Use of corticosteroids is controversial in the management of fungal endophthalmitis. The anti-inflammatory properties of corticoosteroid help modulate the inflammatory response to infection and maintain the structural integrity of the globe.

Table 11.3 Common antifungal agents used to treat fungal endophthalmitis (adapted from [27])

Anti-fungal	Class	Mode of action	Route of administration	Systemic dose	Ocular bioavailability on systemic treatment	Intravitreal dose (0.1 ml)	Preparation of intravitreal dose	Range of activity	Drawbacks
Amphoterycin B	Polyene	Changes cell membrane permeability by sterol binding	Intravenous, Intravitreal	0.5–1 mg/Kg	Poor	0.05 mg	Dilute 50 mg vial with 10 ml distilled water. Draw 0.1 ml and add 0.9 ml normal saline to make 1 ml. Inject 0.1 ml of this mixture	Broad spectrum, drug of choice for severe invasive fungal infection	Renal toxicity

(continued)

Table 11.3 (continued)

Anti-fungal	Class	Mode of action	Route of administration	Systemic dose	Ocular bioavailability on systemic treatment	Intravitreal dose (0.1 ml)	Preparation of intravitreal dose	Range of activity	Drawbacks
Voriconazole	Triazole	Inhibits ergosterol synthesis causing an increase in fungal cell membrane permeability	Oral, intravenous, intravitreal, topical	Oral: 200 mg every 12 h; IV: 6 mg/Kg every 12 h for a day followed by maintainance dose 4 mg/Kg 12 hourly	Excellent	0.1 mg	Dilute 200 mg vial with 20 ml distilled water. Draw 0.1 ml and add 0.9 ml normal saline to make 1 ml. Inject 0.1 ml of this mixture	Broad spectrum, including fluconazole resistant *Candida glabrata* and *Candida krusei*	Hepatotoxicity
Fluconazole	Triazole	Inhibits ergosterol synthesis causing an increase in fungal cell membrane permeability	Oral	200–400 mg per day single dose	Excellent	Not available	Not available	Active against *Aspergillus*	Gastrointestinal side effects, not effective against *Candida glabrata* and *Candida krusei*

Itraconazole	Triazole	Inhibits ergosterol synthesis causing an increase in fungal cell membrane permeability	Oral	200–400 mg/day in two divided doses	Poor	Not available	Not available	Active against *Candida*, Cryptococcus, and *Aspergillus*	Hepatotoxicity and GI disturbance
Ketoconazole	Imidazole	Inhibits ergosterol synthesis causing an increase in fungal cell membrane permeability	Oral	200–800 mg/day in divided doses	Poor	Not available	Not available	Limited activity against Aspregillus	Hepatotoxicity and drug interactions

While this is often considered in bacterial endophthalmtis, the mode of application in fungal endophthalmitis is a matter of debate. Topical corticosteroids are contraindicated in fungal keratitis, but intravitreal dexamethasone injection could be considered in fungal endophthalmitis [28].

Pars plana vitrectomy helps remove the organismal load and inflammatory end products from vitreous and allows better antifungal antibiotic distribution in the eye. As the visibility of retina is obscured by dense vitreous exudates, a careful vitreous dissection is done with the sole aim of debulking as much of vitreous as possible. A complete vitrectomy is better avoided to avert the risk of retinal injury during vitrectomy.

Topical natamycin, a polyene, is the only Food and Drug Administration (FDA)-approved and commercially available topical antifungal. It has good efficacy against filamentous fungi but does not penetrate well into the cornea. Additionally, it forms precipitates upon instillation and degrades easily, requiring storage in a dark container. Topical amphotericin B is commonly used in the management of fungal keratitis, but it requires preparation by a compounding pharmacy. Topical voriconazole in contrast has been shown to penetrate cornea well when applied topically and exceed or meet MIC_{90} levels in vitreous for most pathogens [29].

Treatment Outcome

Post-operative fungal endophthalmitis with presenting vision worse than hand motions do not gain functionally useful vision following treatment. Despite intensive therapy more than half progress to phthisis [7]. Most studies have followed the EVS guidelines [30] in post operative cases—pars plana vitrectomy when vision is worse than hand motions and tap-injection when vision is better than hand motions. In one large study, eyes undergoing pars plana vitrectomy had better post treatment vision than those did not undergo vitrectomy, but was not statistically significant [9]. The other study that tried to determine the role of early vitrectomy in fungal endophthalmitis found that it was not the lone vitrectomy that resulted in good treatment outcome but a strong clinical suspicion of fungal etiology and institution of prompt antifungal treatment which resulted in good visual and structural outcome [31]. As clinical differentiation of fungal from bacterial endophthalmitis is difficult most of the times, it is recommended to add intravitreal antifungal antibiotics to the empirical combination of antibacterials and corticosteroids during the primary intervention, in geographical regions where incidence of postoperative fungal endophthalmitis is high [31]. Few other risk factors that determine the final visual outcome are corneal involvement, trauma and infection by *Aspergillus* species [7].

Frequently Asked Questions

1. *What are the clinical clues to differentiate fungal endophthalmitis from bacterial endophthalmitis?*
   A: Intense conjunctival congestion disproportionate to the corneal involvement or anterior segment findings, dry appearing hypopyon and anterior chamber exudates, pearl string like arrangement of vitreous exudates are some of the clinical features of fungal endophthalmitis.
2. *What is the most common fungal pathogen in exogenous endophthalmitis in India?*
   A: *Aspergillus* species.
3. *What are the risk factors for poor visual and structural outcome?*
   A: The risk factors that determine the final visual outcome are presenting vision worse than hand motions, corneal involvement, trauma, *Aspergillus* infection and delay in institution of antifungal therapy.
4. *What is the preferred antifungal agent for treatment of exogenous fungal endophthalmitis?*
   A: Voriconazole, because it can be administered topically, intravitreally, orally and intravenously. It is effective against most *Candida*, *Aspergillus* and *Cryptococcus* species.
5. *Can corticosteroids be used in treating fungal endophthalmitis?*
   A: Usually no, unless the identified fungus is sensitive to the intravitreally injected anti fungal antibiotics. This situation also calls for caution. When used, dexamethasone could be the right choice because of its very short half life in vitreous.

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The Swamp Monster

Fungal Infection that Responds to Antibacterial Antibiotic

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A 35-year old lady was referred with intractable keratitis of 2 months duration. She had undergone a therapeutic penetrating keratoplasty 10 days prior and was on topical antifungals, antibacterial, and antiglaucoma medications. A corneal scraping from the referring physician had reported aseptate fungal mycelia and gram-positive cocci. Her vision was hand movements (with accurate projection of rays). She had an edematous graft with 16 intact sutures with a dense infiltrate at the graft host junction extending into the graft-host bed along with endo-exudates (Fig. 1, top middle). Her intraocular pressure was digitally high. Ultrasound B-scan of the posterior segment showed a few low reflective membranous opacities.

A diagnosis of a probable recurrence of infection at the graft host junction and host bed was made and a therapeutic penetrating keratoplasty was performed combined with an extra capsular cataract extraction (ECCE). The corneal button sent for microbiological investigation was aseptically cut into four pieces and inoculated on to sheep blood chocolate agar, brain heart infusion broth, Sabouraud dextrose agar (SDA) and non-nutrient agar with *Escherichia coli* overlay. All media were incubated at 37 °C for 1 week save the SDA which was incubated at 27 °C for 2 weeks. Colourless, flat, imperceptible, feathery fungal growth was seen on chocolate agar around the sample (Fig. 11.1.1,) after 24 h of incubation. Fungal growth was also seen in brain heart infusion broth and non-nutrient agar after 24 h but there was no growth on SDA after 2 weeks of incubation. The growth on chocolate agar was identified as *Pythium insidiosum* by zoospore formation on the sixth day post keratoplasty.

Postoperatively the patient had an intense anterior chamber inflammation with a suspicious lesion at 6 O'clock in the anterior chamber with a poor fundal glow and vitreous exudates (Fig. 11.1.1,, top right). A parsplana core vitrectomy was done on the third postoperative day; intravitreal voriconazole 100 μg in 0.1 ml was injected, and repeated two times, on post vitrectomy day 3 and 7. Post vitrectomy she was treated with hourly topical natamycin 5%, cycloplegics, oral ketoconazole 200 mg twice a day and antiglaucoma medication. Topical steroids were started on the fifth day after surgery. On the tenth postoperative day, the intraocular inflammation reduced probably in response to the topical steroids though the suspicious lesion at 6 O' clock in the anterior chamber persisted. We realized from the published reports and our experience that *Pythium* keratitis does not respond to available antifungal medication. The literature search indicated that *Pythium* is more (approximately 100 times) susceptible to certain antibacterial agents compared to antifungals.

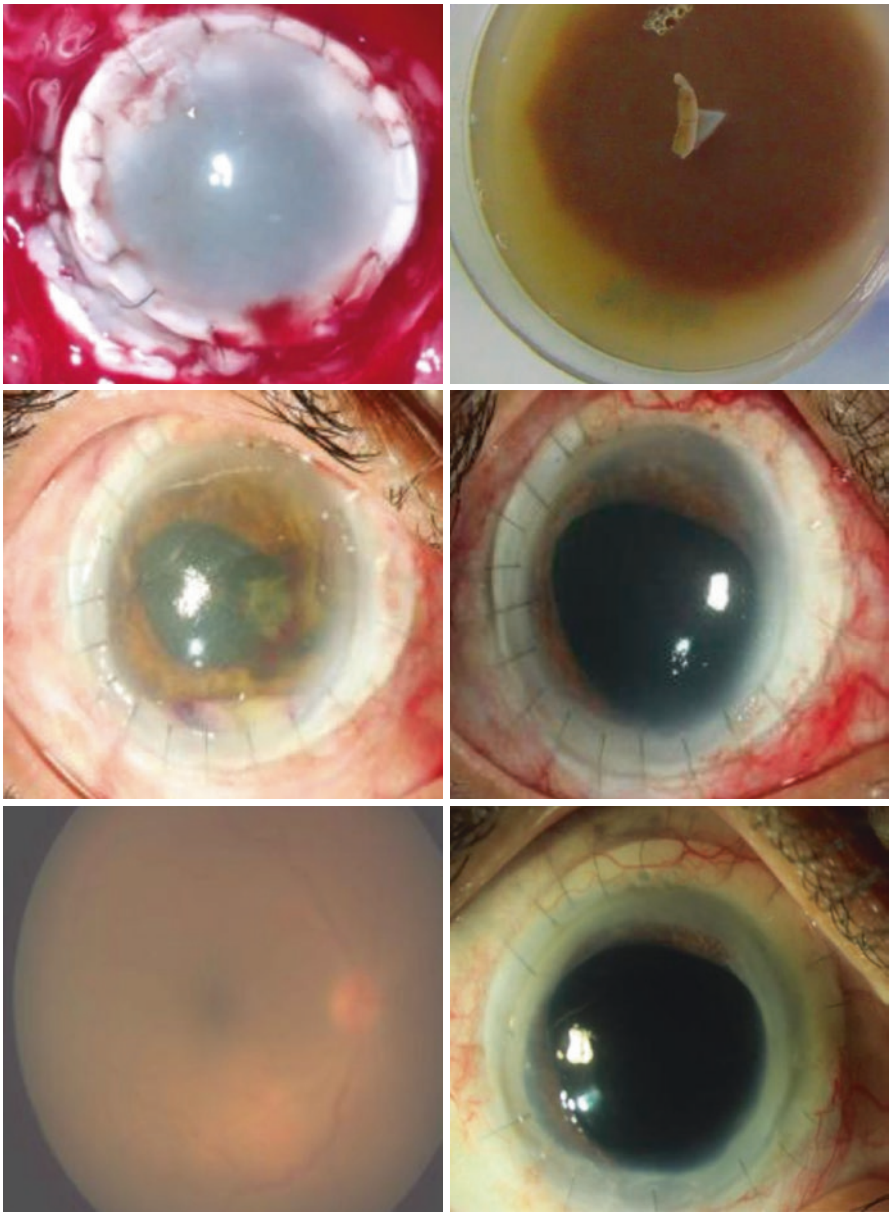

Fig. 11.1.1 *Top left*—at presentation there was recurrence of keratitis with infiltration at the host bed; *Top right*—Chocolate agar inoculated with corneal button showing slight feathery growth on the right edge 24 h after incubation at 37 °C; *Middle left*—the anterior chamber exudate at 6 O' clock persists even 10 days after repeat therapeutic penetrating keratoplasty; *Middle right*—a clear graft with no recurrence of exudates in the anterior chamber and *Bottom left*—a good view of the fundus up to the third order blood vessels 7 days after the intravitreal linezolid injection, localized iris excision and local cryotherapy. *Bottom right*—a clear graft 3 months post op with 20/50 visual acuity with contact lens and endothelial cell count of 2783 cells/mm^2

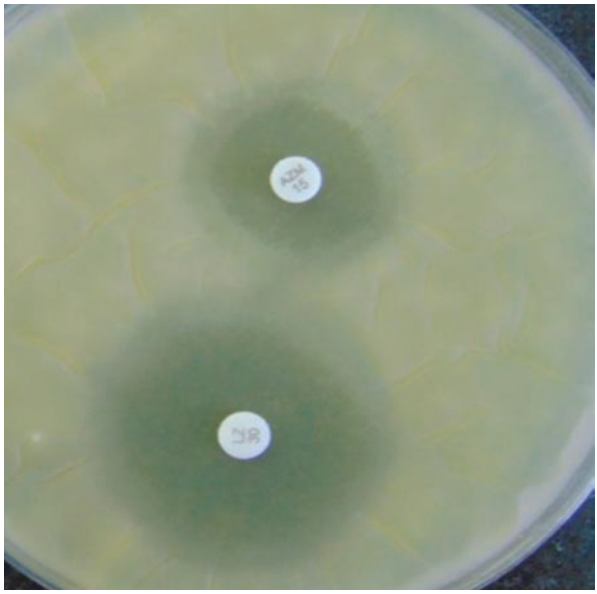

Fig. 11.1.2 Disc diffusion test done on *P. insidiosum* isolated from the corneal button of the patient shows 24 mm zone of inhibition around linezolid and 21 mm around azithromycin (Mueller Hinton agar with discs containing 30 µg linezolid and 15 µg azithromycin, incubation—37 °C, 72 h)

Based on these information, we tested *P. insidiosum* isolated from the corneal button of this patient against certain antibiotics such as linezolid, azithromycin, chloramphenicol, amikacin and gentamicin using the disc diffusion method. Commercially available antibiotic discs from HiMedia, India were used for the purpose. Measured quantity of the zoospores was inoculated on Mueller Hinton agar followed by placing of antibiotic discs and incubation at 37 °C for 72 h. Large zone of inhibition were noticed around linezolid (24 mm) and azithromycin (21 mm) discs (Fig. 11.1.2).

Encouraged by the results we performed an excision of the iris from 5 to 6 O' clock along with the exudate, applied cryo over the adjacent sclera and injected linezolid 200 µg/0.1 ml and voriconaole100 µg/0.1 ml intravitreally. A week later, her symptoms improved dramatically. Her best- corrected visual acuity improved to 20/80 and intraocular pressure remained within normal limits without oral acetazolamide (Fig. 11.1.1, bottom left). At her last visit her vision further improved to 20/50 with soft contact lens (aphakic eye) (Fig. 11.1.1, bottom middle and right). The graft was clear and the specular count of the graft was 2783 cells/mm^2.

Comments

Pythium is a relatively rare and probably an under diagnosed cause of fulminant keratitis. Numerous members of the *Pythium* spp. are plant pathogens; *Pythium insidiosum* and recently *Pythium aphanidermatum* are the only species known to

infect humans and mammals. *Pythium* species inhabit aquatic and moist soil environments. Pythiosis is endemic in Thailand. The environmental niche for *P. insidiosum* may be expanding, probably as a result of environmental changes like deliberate flooding of rice fields or irrigated landscape development with case reports of equine *Pythium* infections in California. Systemic pythiosis is usually seen in association with haemoglobinopathies. Ocular pythiosis begins usually with keratitis and progresses to scleritis and endophthalmitis that may need an evisceration unless early therapeutic penetrating keratoplasty with large margins is performed.

Pythium insidiosum belongs to the class Oomycota of the kingdom Stramenopila. Microscopically *P. insidiosum* develops mycelium like fungi, but it is not a true fungus. Unlike fungi which have chitin in their cell walls and ergosterol in their cell membranes, *Pythium* has cellulose in its cell wall and lacks ergosterol in its cell membrane. This lack of ergosterol is the reason for its poor response to the currently available antifungal medication. Therefore, wide surgical excision (radical surgery) remains the mainstay of treatment. Immunotherapy is the emerging adjuvant therapy with variable success.

To the best of our knowledge this is the first patient with recurrent *Pythium* keratitis with possible intraocular extension treated with intravitreal Linezolid and Azithromycin with good outcome. Clinically anti-pythium antibodies have been used to diagnose infection but have a very low yield in ocular disease. Molecular tools, such as internal transcribed spacer (ITS) or 28S rDNA region sequencing may be used to confirm the identity of the organism. Loreto et al. have shown antibacterial drugs like linezolid, azithromycin, minocycline and tigecycline inhibit the *in vitro* growth of *Pythium insidiosum* at concentrations 100 times lower than the antifungal drugs. These drugs are protein synthesis inhibitors which act on prokaryotic ribosomal RNA to prevent protein synthesis. Linezolid has 100% oral bioavailability and exhibits a concentration dependent killing. Studies have shown a good aqueous and vitreous penetration of systemically administered linezolid. Functional and histopathological safety in rabbits of intravitreally injected linezolid have been proven. This can be used as an adjunct to intraocular or topical drug in ocular pythiosis. This drug may also be tried in systemic pythiosis.

Intravitreal Preparartion of Linezolid

Linezolid infusion (Glenmark Pharmaceutical Ltd., Ahmedabad, India) is available in 2 mg/ml solution. Withdraw 0.1 ml directly from the infusion bottle; this contains 200 μg/0.1 ml for intravitreal injection without further dilution.

Suggested Reading

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Chapter 12
Endophthalmitis in Newborns and Preverbal Children

Subhadra Jalali

Endophthalmitis in newborns and preverbal children constitutes only a small proportion of all endophthalmitis visiting a hospital. While most principles and practice of evaluation and managing endophthalmitis in this vulnerable group are similar to other cases of endophthalmitis described in this book, important considerations are highlighted in this chapter.

Neonatal and infantile endophthalmitis is mostly from an endogenous source of infection and is the main focus of this chapter. Rarely it could be following post-accidental and non-accidental trauma, post-intraocular surgery, or microbial keratitis especially after keratomalacia, gonococcal keratoconjunctivitis, or congenitally anesthetic cornea. Trauma remains the most important cause in older children followed by post-intraocular surgical infections that are dealt with elsewhere in this book and are mostly similar to adult cases.

Endogenous endophthalmitis in neonates is a rare clinical situation and constitutes 0.1–4% of all endogenous endophthalmitis cases [1, 2]. In the USA, the incidence of endophthalmitis reported from one neonatal intensive care unit (NICU) was 0.14% of all admitted babies [3]. Endogenous endophthalmitis is more common in East Asia and India with large series reported that included the neonates [2, 4].

Clinical Presentations and Common Organisms

Endophthalmitis in newborns presents as two distinct clinical presentations, and a third rare type mostly depending upon the virulence of the causative organisms and treatment given. A fulminant, acute inflammation (Fig. 12.1), which is mostly, though not always, due to virulent gram-negative organisms, is the commonest. The causative organisms include *Pseudomonas*, *Klebsiella*, *E. coli*, *Acinetobacter*, etc.

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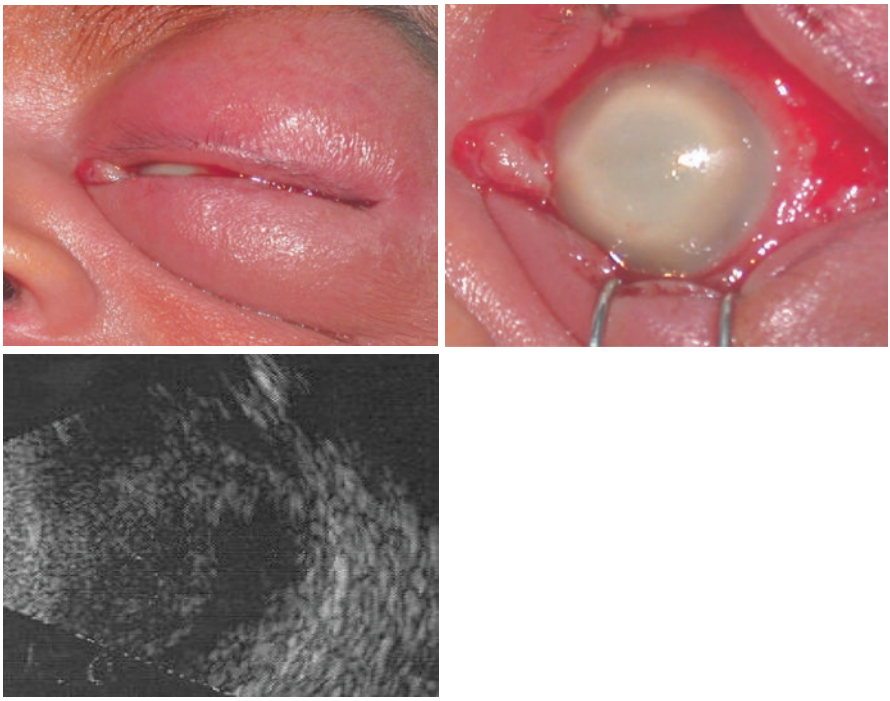

Fig. 12.1 Fulminant gram-negative neonatal endogenous endophthalmitis. Note periorbital edema (*top left*), conjunctival chemosis, corneal edema, and exudates in anterior chamber (*top right*). Ultrasonography shows vitreous echoes, choroidal thickening, and low reflective retinal detachment (*bottom left*)

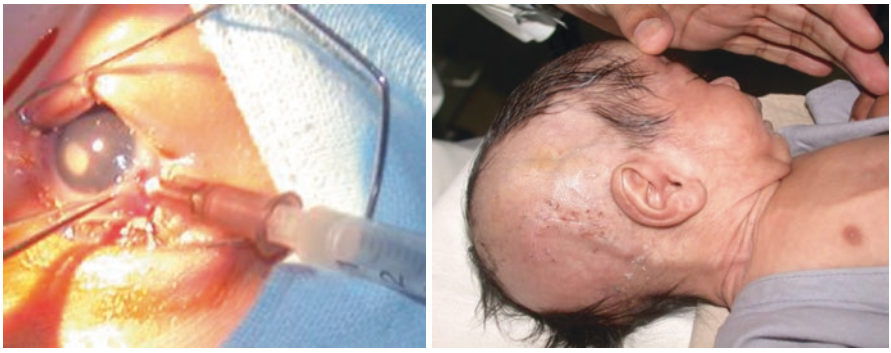

Fig. 12.2 Ventriculoperitoneal (VP) shunt induced *Fusarium* endophthalmitis. *Left*—note leucocoria and lens abscess. Aqueous and vitreous tap under topical anaesthesia, followed by intraocular antibiotic injection, was done in this patient

[1–4]. The gram-positive organisms include methicillin-resistant *Staphylococcus aureus* (MRSA), *Bacillus* and *Streptococcus*, and rarely vancomycin-resistant *Staphylococcus epidermidis* (VRSE) [5]. Rare cases with fulminant picture may be of fungal etiology such as *Fusarium* (Fig. 12.2) from a ventriculoperitoneal (VP) shunt [2] or virulent *Herpes simplex* virus (HSV) infections [3].

The second clinical picture is of a very low-grade retinal infiltrate, diagnosed on routine retinal screening. This presents as a single or multiple yellow-white lesions varying from pinhead to few millimeter size, minimally elevated from the retinal surface or as a small subretinal abscess with indistinct borders. The most common causative organism is *Candida albicans and Candida tropicalis* (Fig. 12.3). Vitritis is

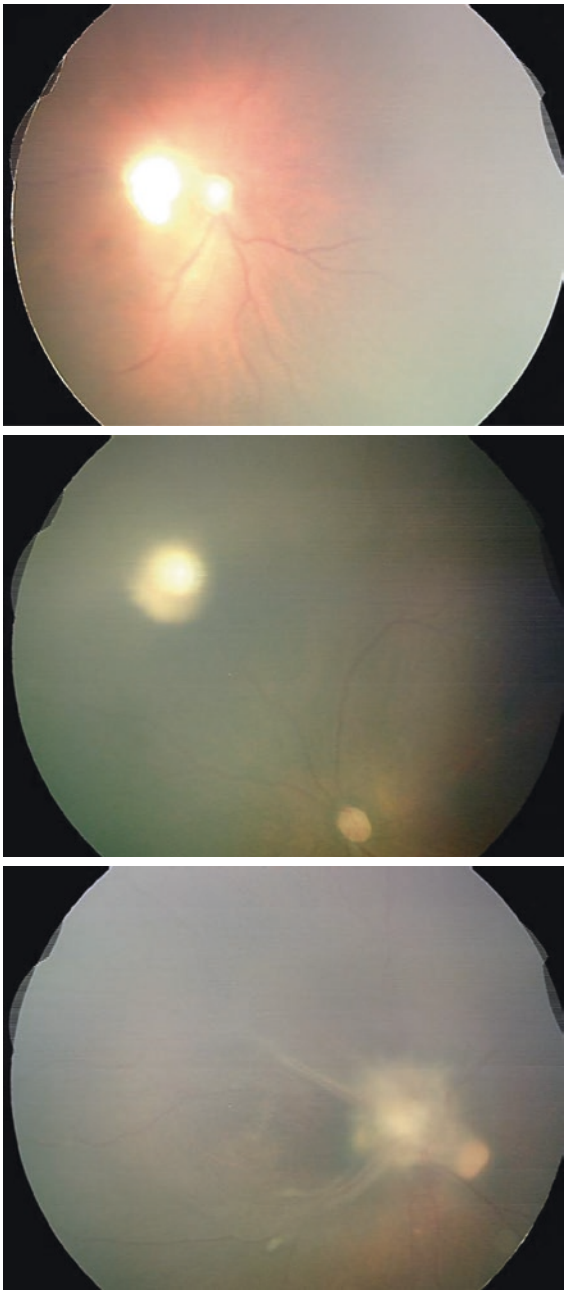

Fig. 12.3 Non-fulminant endophthalmitis. Fungal retinitis: *top* and *middle*—presumed *Candida*, early and active phase showing typical retinal infiltrates. *Bottom*—advanced stage with vitreopathy and retinal folds that needs urgent lens-sparing vitrectomy without any subretinal treatment

minimal or absent to start with but gradually becomes manifested as the disease progresses. This characteristic clinical diagnosis is sufficient to start antifungals as the lesions are very classic and typical. Low-grade viral retinal infections from HSV and cytomegalovirus (CMV) also start as mild to moderate diffuse retinitis without vitritis (Fig. 12.4) and later can progress to severe vitritis and sometimes keratitis [6].

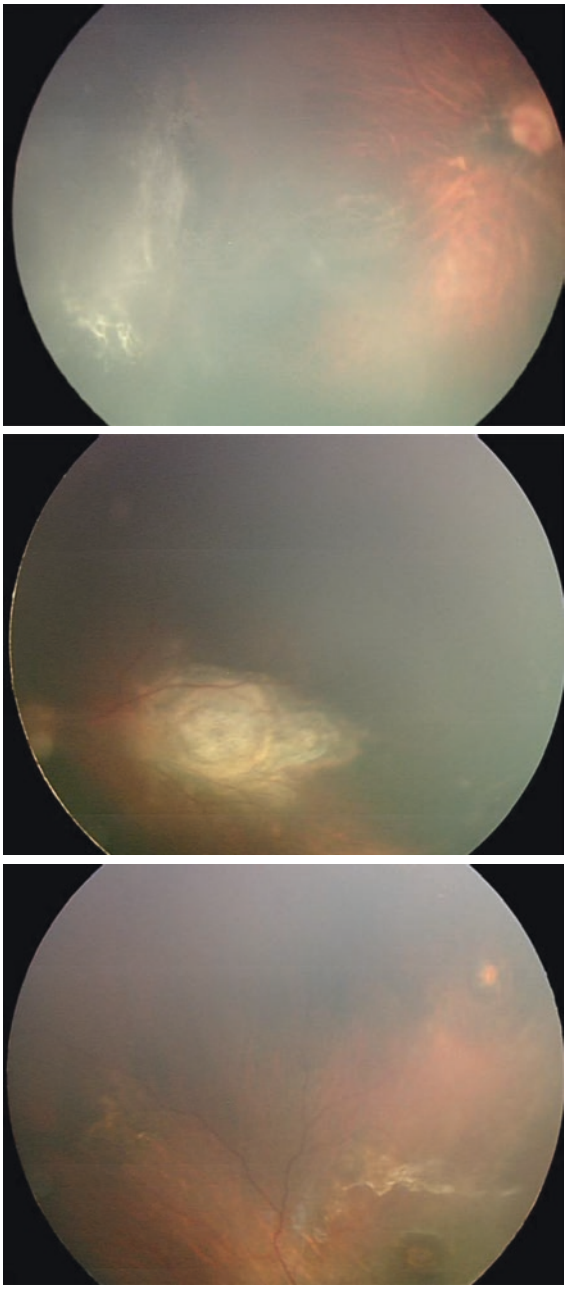

Fig. 12.4 Viral retinitis (CMV/HSV) always shows some chorioretinal scars in addition to retinitis

Rarely a third type of clinical picture, partially resolved bacterial endogenous endophthalmitis presents as a less severe infection, after having received parenteral antibiotics during septicemia. These present mostly as a low-grade partly organized subretinal abscess (Fig. 12.5) or vitritis or organized leucocoria (Fig. 12.6) resembling a pseudoglioma due to retinal necrosis and retinal detachment. Another rare clinical presenta-

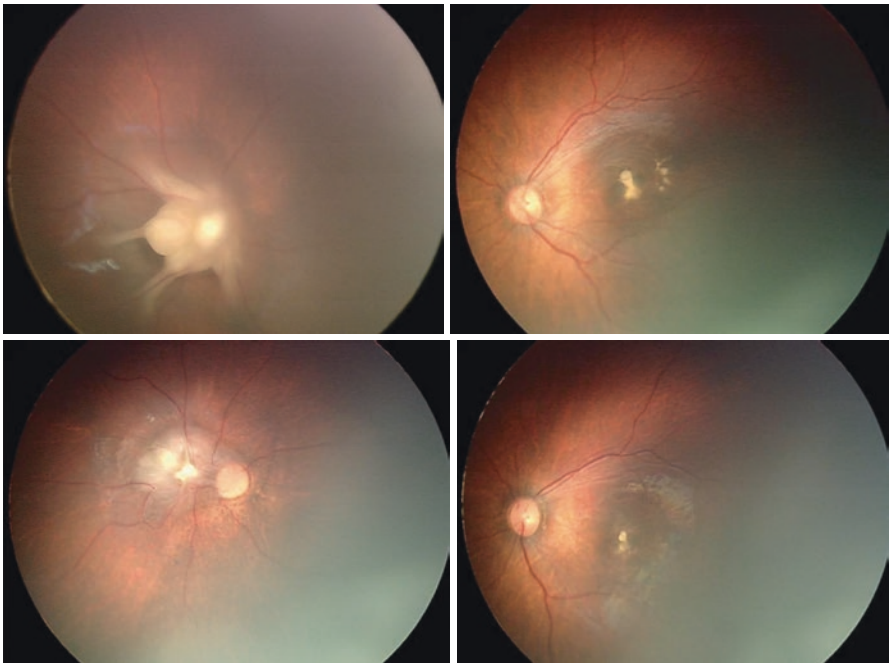

Fig. 12.5 Partially resolved endophthalmitis. Blood culture: *E coli*. *left panel*—preoperative (Top *left*) and post lens-sparing vitrectomy (Bottom *Left*). *Right panel*—Preoperative (Top *Right*) and post-systemic antibiotics (Bottom *right*)

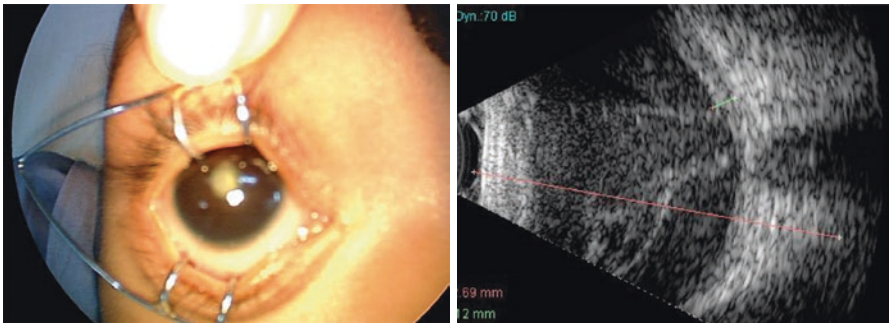

Fig. 12.6 Partially resolved endophthalmitis with systemic antibiotics noted few days after an acute systemic septic episode. This child presented with leucocoria and a shrunken globe resembling a pseudoglioma (*left*). The child was referred as a case of retinoblastoma. The ultrasonography shows no mass but showed a degenerated retinal detachment with low-intensity echoes in vitreous and subretinally—a prephthisical stage (*right*)

tion is a localized anterior chamber granuloma or a very focal iris abscess (authors' experience) that can respond to systemic antimicrobials (anterior endophthalmitis).

Risk factors: Prematurity with low birth weight and hospitalization has been associated in 80% babies presenting with neonatal endophthalmitis [1–4]. Rarely, healthy and normal-weight term babies without any apparent risk factor get such infections [2–4]. The common risk factors are listed in Table 12.1. In the USA, over the years, possibly due to implementation of strict asepsis protocols and attention to the risk factors, there has been a declining incidence of neonatal endogenous endophthalmitis; it reduced from 8.7 per 100,000 babies in 1986 to 4.42 per 100,000 babies in 2006 [7]. In a prospective case series of neonatal candidemia with a prevalence of 1.1 per 100 NICU discharges, endophthalmitis was seen in 2 of 20 babies where eye was evaluated [8].

Diagnostic criteria: Cultures may not be always positive. Hence only laboratory-based confirmation is not adequate to identify all infected endophthalmitis cases, especially of endogenous origin [1–7]. Diagnostic criteria are given in the Table 12.2.

Table 12.1 Susceptibility and risk factors: [1–4, 7]

• Premature and low birth weight (especially less than 1500 g)
• Compromised immune status
• Hospital admission
• Indwelling catheters, infusion pumps, ventilators, implants
• Poor handwashing and hygiene of healthcare workers not practicing good barrier nursing
• Umbilical sepsis
• Bacteremia/candidemia
• Blood transfusion
• Pneumonia/septic abscesses/meningitis
• Cross contamination from other infected babies
• Nursery infection outbreaks such as *Candida, Meningococcus*, etc.

Table 12.2 Diagnostic criteria for neonatal endophthalmitis

Any two of the following five clinical and laboratory features can be considered as a case of neonatal endogenous endophthalmitis:
1. Inflammation of intraocular tissues where except for an infective etiology, no other underlying cause is detected
2. Clinical involvement of retina or vitreous showing typical features of exudation and/or inflammation
3. Any intraocular sample shows significant growth on culture
4. Any of the body tissues/fluid shows significant growth or microbial organisms. Common samples include blood, urine, umbilical cord stump swab, swab from any abscess, etc. in association with ocular inflammation
5. PCR is positive for eubacterial or panfungal or specific viral DNA from ocular sample in presence of ocular inflammation

Investigations

1. All cases suspected to have neonatal and infantile endophthalmitis should have a careful ocular ultrasonography (USG-B) scan with corresponding A-Scan. Endophthalmitis eyes in early stages may have normal USG but in most cases will show low-intensity echoes. USG helps to confirm diagnosis and identifies poor prognostic indicators like retinal detachment, choroidal detachment, membranous echoes (Fig. 12.1, 12.6), and dense echoes filling most of the vitreous cavity. In all cases careful USG including immersion scan should also be done at low gain to evaluate all areas for any mass lesions or calcifications that would suggest an underlying retinoblastoma, which can masquerade as orbital cellulitis or endophthalmitis (Fig. 12.7). If possible, this is done preferably under general anesthesia as sometimes in a crying and struggling child one may miss scanning some areas that contain a hidden underlying tumor. Intraocular cysticercosis that can masquerade as endophthalmitis is also very well diagnosed by USG in most cases. USG is much more sensitive and specific than CT scan or MRI in the diagnosis of neonatal and pediatric endophthalmitis.
2. Find source of infection: Detailed antenatal history must include episodes of fever, septicemia, or vaginal discharge or eruptions in the mother, the mode, and setting of delivery including rural or home deliveries and puerperal sepsis in mother, details of postnatal hospitalization, culture from tubes/ cannulas, etc. for any infective focus like septic arthritis, meningitis, liver abscess, pneumonia, blood cultures, or cultures from urine or other infected body fluids. Evaluation of umbilicus may reveal the source (Fig. 12.8). History should also record any septic epidemic in the nursery at the time of stay of the index case. Thorough systemic evaluation is essential. Past culture and neonatal course reports should be reviewed in consultation with the child healthcare givers.
3. Detailed evaluation of fellow eye including dilated indirect ophthalmoscopy fundus examination at each visit, both in the clinic and whenever the opportunity arises, under general anesthesia additionally, is necessary (Fig. 12.5).

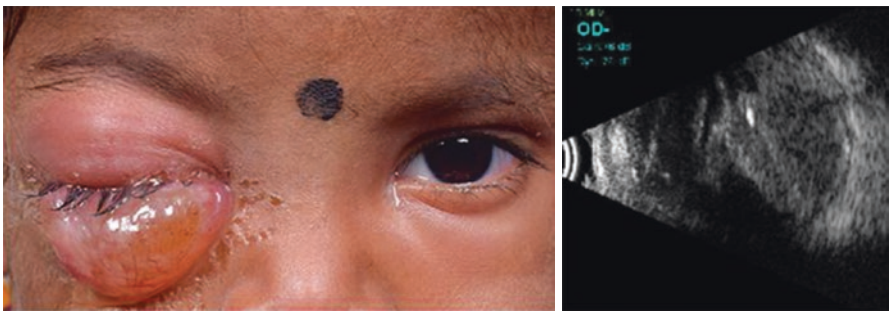

Fig. 12.7 Retinoblastoma can present as orbital cellulitis. *Left*—orbital cellulitis with lid edema, conjunctival chemosis; *right*—USG showing large intravitreal mass with calcification and choroidal thickening. Courtesy: Swathi Kaliki, MD

4. Screen other twin/triplets nursery babies. Examination of mother including vaginal swabs, when indicated, helps.
5. All babies with candidemia/bacteremia need dilated fundoscopy, especially if having prolonged infection for more than 2 weeks.
6. All premature babies also need regular fundoscopy for associated ROP; this will need comanagement.
7. Baby must be co-evaluated for other systemic problems that can be life threatening such as septicemia, meningitis, endocarditis, peritonitis, septic liver abscess, etc.

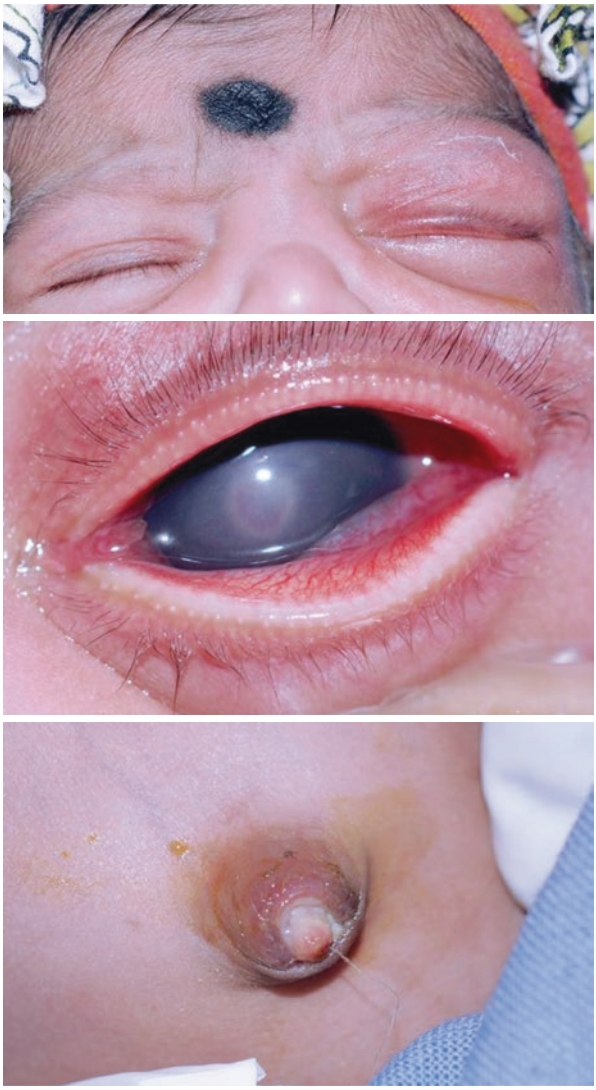

Fig. 12.8 Newborn showing left eyelids edema (*top*), conjunctival congestion, corneal edema, nearly flat anterior chamber, and leucocoria with lens abscess (*middle*). Umbilical sepsis was a possible source of infection (*Bottom*)

Differential diagnosis: Endogenous endophthalmitis can mimic many other ocular conditions in newborns and small babies. Each of these conditions need attention to clinical, laboratory, imaging, and ancillary testing to arrive to a reasonable diagnosis. Table 12.3 provides other differential diagnosis.

Management: In absence of any large randomized trials or large series of cases of this rare condition, the broad principles of endophthalmitis management are the same in neonates and small children as in adults. These include prompt clinical and microbiological diagnosis and initiation of empirical intravitreal antimicrobials followed by specific modification of antimicrobials based on clinical response and laboratory diagnostic reports. There are however numerous challenges specific to neonatal and infantile endophthalmitis cases (Table 12.4).

Modifications are needed from adult protocols to address some of these challenges. For example, babies who are sick and not fit for general anesthesia could

Table 12.3 Differential diagnosis of endogenous endophthalmitis in neonates and infants

Congenital nasolacrimal duct obstruction
Mucopurulent conjunctivitis including *gonococcal*
Infectious keratitis
Orbital cellulitis
Retinoblastoma
Congenital cataract
Primary hypoplastic primary vitreous (PHPV), other pseudogliomas like retinal dysplasia, etc.
Differential diagnosis in preverbal children beyond infancy:
All above and
trauma, toxocariasis, cysticercosis, and keratomalacia

Table 12.4 Challenges in management of endogenous endophthalmitis in small children [2–4]

• Fragility of child and unfit for general anesthesia
• Systemic co-morbidity especially cardiac (PDA), respiratory (pneumonia), neurological (meningitis/encephalitis), and hematological (anemia, thrombocytopenia)
• Retinal detachment and necrosis preexisting due to fulminant bacteria
• Unilateral aphakia and dense amblyopia following surgery
• Glaucoma/retinal detachment/hypotony after surgery
• Concomitant retinopathy of prematurity (ROP) that can worsen rapidly
• Systemic and ocular cultures may be sterile as patient may already have received systemic antimicrobials or sample may be too small
• Multidrug resistant nosocomial infections
• Logistics of coordination with neonatologists/pediatricians and transportation of babies to ophthalmology operating room that may be remote from the child care facility
• Lack of clinical trial/large series/meta-analysis data. Lack of consensus statements in literature
• Lack of drug dosing information for intravitreal and sometimes for systemic therapy
• No neonatal dose eye drops information or formulations available
• Potential for neonatal drug toxicity, but no literature readily available
• Delayed referral

undergo aqueous/vitreous tap under topical anesthesia with intravitreal antibiotics (and steroids, if so considered) in cases presenting with fulminant endophthalmitis (Fig. 12.2). This provides adequate identification of infecting agent and appropriate antibiotic selection; it also provides control of infection that helps to avoid evisceration even in eyes presenting as panophthalmitis. Since most cases are nosocomial and multidrug resistant, microbiological work-up becomes essential. In fungal retinal infiltrate, only intravitreal amphotericin B is given (half adult dose), and no sample is taken as the anterior vitreous or aqueous will not show any results in this scenario, and treatment is based on the typical clinical picture. If child is fit for general anesthesia, then depending on clinical severity, lens-sparing vitrectomy or vitrectomy with lensectomy is done with sclerotomy at a distance of 1.0 mm from limbus in neonates and infants due to underdevelopment of pars plana in these eyes. In one of the largest published series on neonatal endophthalmitis, all eyes with *Candida* infection could be salvaged by intravitreal amphotericin B under topical anesthesia followed promptly by lens-sparing vitrectomy (Fig. 12.3, 12.5) as soon as vitritis developed [2].

Unlike adults, in neonates, vitreous involvement can lead to rapid folding, stretching, and anterior elevation of the retina (Figs. 12.3 and 12.5). Early surgical intervention can help to flatten these folds before they get elevated far enough to touch the lens, which would necessitate lensectomy. The principles are similar to vitrectomy for ROP-related stage 4A detachments, that progress to require lensectomy if not operated urgently. Once lensectomy is needed, the prognosis becomes poor not only due to challenge of managing a unilateral aphakia and amblyopia at this young age but also due to the high risk of secondary glaucoma [4]. Hence early surgery appears more favorable [2].

Results: Most gram-negative fulminant bacterial cases are reported to resolve with phthisis bulbi or need evisceration. Evisceration can be avoided by managing with intraocular antibiotics and steroids in the eyes that present with fulminant infection [2]. Occasional good outcomes are reported in few cases of fulminant infection, especially those who are diagnosed and managed by immediate surgery. This requires vigilance, high degree of suspicion by treating pediatrician, and a whole lot of coordination to get baby rapidly fit and taken up for surgery [5]. We reported a large series of 31 eyes of 26 babies of neonatal endophthalmitis; in this series all the eyes with suspected *Candida* could be salvaged with good visual outcomes while all the bacterial fulminant eyes became phthisical, but none progressed to evisceration [2]. High mortality from septicemia or meningitis has been reported in some series, and this would depend on the causative organism and clinical situation [8–10]. In a study on long-term outcomes of neonatal *Candida* endophthalmitis treated by systemic therapy alone (intravenous amphotericin B/oral fluconazole), 7 of 11 eyes achieved good outcomes. All three eyes that had poor outcome were due to vitreous traction and macular lesions that did not undergo prompt surgery [11]. In some cases, fungal infections can present as a lens abscess that is possibly a result from hematogenous spread through the persistent tunica vasculosa lentis in premature babies [12]. These eyes have poor outcomes due to inability of systemic drugs to reach the poorly vascularized lens substance as the hyaloid system regresses,

leaving a nidus of infection within the substance of the lens [12]. Prompt lensectomy and intravitreal antifungals would be needed in such cases [12].

Few cases of coexisting ROP in the setting of intraocular infection have been reported. There may be more progression of ROP due to inflammatory cytokines and angiogenic factors [12]. Treatment would also be challenging in view of media haze. Successful management of such cases by surgery or laser has been reported.

Guidelines for surveillance: All babies who are in hospital and diagnosed as having candidemia/bacteremia need regular fundoscopy to detect any ocular spread. This could be weekly in case of candidemia [12] and daily in case of gram-negative septicemia. Any inflammation around eyes (lid edema/erythema, conjunctival injection, ocular discharge) requires pupil dilatation and fundoscopy. The widespread practice of using empirical antibiotic eye drops with a provisional suspicion of a "simple mucopurulent conjunctivitis" without a "red glow" could lead to a delayed diagnosis and loss of a salvageable eye.

Frequently Asked Questions

1. *Should vitrectomy/intravitreal antimicrobials be done early or late in neonatal endophthalmitis when retina is visualized?*
   A: We believe that under topical anesthesia, neonates can receive intravitreal antimicrobials, just like adults, and need not wait for systemic status to improve for general anesthesia fitness. This allows lens-sparing vitrectomy/intravitreal approach early. Delaying treatment could necessitate lensectomy that could progress to unilateral amblyopia and glaucoma.
2. *When, how often and who should do fundoscopy in babies diagnosed to having bacteremia/candidemia in the nursery.*
   A: All babies with systemic infection should undergo mandatory dilated indirect ophthalmoscopy at least weekly in active phases of infection and promptly in case of any redness or sign of ocular inflammation during follow-up.
3. *When, how often and who should do fundoscopy in the nursery in babies who get red eye and /or mucopurulent discharge from the eyes?*
   A: All such babies need a red glow fundus test by physician after dilating pupils with 1% tropicamide on daily rounds. Any suspicion should prompt urgent evaluation by a competent ophthalmologist using indirect ophthalmoscopy.

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Chapter 13
Cluster Endophthalmitis

Mudit Tyagi

Endophthalmitis is one of the most serious and dreaded complications of intraocular surgeries, and although the incidence is low, the ocular morbidity of postsurgical endophthalmitis is significant. The incidence of postoperative endophthalmitis has been reported to be 0.14–0.16% or 1 case per 625–730 cataract extractions in one of the reports [1]. Isolated cases of endophthalmitis are not uncommon when large volumes of surgeries are done. These are dealt with in another chapter. However, a cluster of cases requires a more detailed evaluation and understanding. There is a paucity in ophthalmic literature about the incidence of cluster cases. This chapter describes a systematic approach to evaluation, management and outcomes of cluster endophthalmitis.

Definition

A cluster endophthalmitis is defined as occurrence of endophthalmitis much higher than the local incidence pattern [2] or occurrence of two or more cases of infections at a time or the occurrence of repeated postoperative infections under similar circumstances, i.e., with the same surgeon, same staff or the same operating room.

Potential sources of these outbreaks usually include bacterial contamination from the surgical intraocular instruments, irrigating fluids or the surgical environment [3–9]. A systematic review of 27 reports of endophthalmitis outbreaks following cataract surgery between 1985 and 2011 by Pathengay et al. [10] found the two most common causes associated with the outbreaks were contaminated solutions (irrigating fluid, dyes and viscoelastics) and contaminated phacoemulsification machines.

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Most of the literature on outbreaks of cluster infections has been from the Western Hemisphere, and some of the recent reports of cluster endophthalmitis are from India as shown in Table 13.1.

Isolated cases of acute postoperative endophthalmitis cases are usually believed to arise from the patient's own commensal bacteria and are mainly gram-positive cocci. In contrast, gram-negative organisms have been found to be commonly associated with epidemics of cluster outbreaks of acute-onset postoperative endophthalmitis after cataract surgery. *Pseudomonas aeruginosa* is the most common gram-negative organism. It is often associated with nosocomial infections affecting the skin, urinary tract, lungs and heart [10]. Outbreaks of *P. aeruginosa* endophthalmitis are most likely to have an exogenous origin as they are not part of the normal conjunctival flora.

Cluster endophthalmitis has also occurred after the use of anti-VEGF agents, more commonly bevacizumab (Avastin®, Genentech, Inc.), and the outbreak has

Table 13.1 Reported cluster infection in India

Author	Period	Aetiology	Location	No.	Organism
Kenchappa et al. [11]	Jun 2003	Phacoprobe and internal tubings of phacoemulsification machine	Hyderabad, South India	9 Eyes	*Pseudomonas aeruginosa*
Malhotra et al. [12]	Feb 2005–Feb 2006	Not known (three different clusters)	Raipur, Chhattisgarh, Central India	24 Eyes	*Pseudomonas aeruginosa*
Korah et al. [13]	2006	Not known	Vellore, South India	19 Eyes	*Enterobacter amnigenus*
Pinna et al. [7]	Feb–Apr 2008	Phacoemulsifier's internal tubes, the povidone-iodine solution and the operating theatre air conditioning system	Tiruchirappalli, South India	20 Eyes	*Pseudomonas aeruginosa*
Ramappa et al. [8]	Sep 2010	Hydrophilic acrylic intraocular lenses and their solution	Hyderabad, South India	11 Eyes	*Pseudomonas aeruginosa*
NPCB report [14]	Sep 2010	Not known	Mandala, MP, Central India	38 Eyes	**Not known**
NPCB report [14]	Dec 2010	Water used for scrubbing was contaminated	Indore, MP, Central India	18 Eyes	*Klebsiella* sp.
NPCB report [14]	Sept 2011	Contaminated OT trolley and table	Balod, Chhattisgarh, Central India	46 Eyes	*Pseudomonas aeruginosa*
Lalitha et al. [15]	Dec 2011–Mar 2012	Local anaesthetic eye drops	Madurai, South India	13 Eyes	*Burkholderia cepacia*

usually been because of a contaminated batch. Postinjection endophthalmitis is discussed in another chapter in this book.

Management Principles

The aim of management in cases of an outbreak should be:

- Prompt and effective treatment of the endophthalmitis cases
- Reporting to the concerned authorities
- Analysis and identification of the cause
- Implementation of practices to reduce future outbreaks
- Continuous audit of complications, procedures and practice patterns

The medical management of cluster endophthalmitis is no different than the postoperative endophthalmitis and invariably follows the recommendations of the Endophthalmitis Vitrectomy Study (EVS) [16] except that more often these eyes need vitreous surgery.

The management of cluster endophthalmitis does not end with the clinical management of the eyes. It is necessary to probe the cause of such infection and take measures to prevent future recurrences. This process begins with the reporting incident to the hospital infection control committee (HICC). Depending on the number of cases, green/amber/red alert is sounded as follows (Table 13.2).

An amber or red alert may necessitate closure of the operating rooms in order to investigate for the cause of the outbreak.

Tracking Cluster Endophthalmitis

The Royal College of Ophthalmology provides guidelines for investigating and managing outbreaks of endophthalmitis [17].

In general the following protocols and procedures should be adhered to:

- Alert colleagues and make them aware of the cases thus far and recall the patients operated on the same day or in the same operating room(s).
- Inquire about the incidence of any other case(s), and ensure that other patient(s) are fully aware of postoperative danger symptoms.

Table 13.2 Alerts in cluster endophthalmitis

Green Alert	1 case of endophthalmitis is noted, in 1 ≥ 100 cases, or 2 in ≥ 600 cases
Amber Alert	1 case in 75 cases, 2 cases in 300-500 cases, 3 cases in 700-800 cases
Red Alert	2 cases in ≤ 200 cases, 3 cases in ≤ 600 cases, 4 cases in ≤ 800 cases

- The incident forms should be filled and documentation should be done *(A sample incident form is attached at the end of this chapter—Annexe 1 and 2)*
- If receiving multiple cases from another hospital, then their clinical heads and concerned ophthalmologists and hospital administrators should be informed.

Constitute an investigating team involving the hospital consultant microbiologist, ophthalmologists and hospital infection team including the operating room nursing staff, clinical risk managers and hospital managers.

The main areas of investigation as recommended by Anderson et al. [2] are:

1. Operating room environment
2. Pre-, peri- and postoperative practices
3. Instrument cleaning and sterilisation
4. Equipment maintenance
5. Documentation of cases and the irrigating fluids used and other factors

Microbiological Surveillance

The microbiological surveillance does not end in identification of the infecting organism and performing the antibiotic sensitivity profile. It is necessary to prove its link to the case, and this is only possible with molecular methods [5, 7, 8, 11].

Checklist for Investigation of Suspected Outbreak of Postoperative Endophthalmitis

CSSD-(Central Sterile Supply Department) Related Issues

- Autoclave function, its pressure and temperature gauges.
- Reports of recent biological indicators.
- Signaloc usage with every pack.
- Time, steam and temperature (TST) strips with every cycle and recording of its colour change
- Concentration of aseptic solution used to clean instruments.
- Check knowledge of technicians working in CSSD.
- UPS connection for autoclaves.
- Maintenance of register for each autoclave.

Operating Room Administration and Environment

- Operating room ventilation and airflow systems
- Concentration of Bacillocid used for cleaning OR
- Operating room cleaning and carbolisation/fumigation
- Regular microbiology surveillance every month

- If report is unsatisfactory, whether repeat cultures are done after appropriate cleaning
- Personal hygiene of staff and patients

Operating Room Nurse/Assistant-Related Issues

- Whether scrubbing procedure is satisfactory.
- Preoperative skin preparation of the eye with 10% povidone-iodine.
- Preoperative application of 5% povidone-iodine to the patient's lids and conjunctival sac just prior to draping.
- Sterile instruments are used for each case.
- Proper handling of instruments during surgery.
- Batch number and details of the irrigating fluids and all other fluids and dyes used during surgery should be reviewed. Batch number and details of the intraocular lens used in surgeries must be recorded.
- Cleaning of phaco machine to be checked and sterilisation of phaco tubings.

Surgeon-Related Issues that Are Checked

- If more than one case developed endophthalmitis, was it the same surgeon involved in the cases?
- The sequence and surgical log of the the day by the surgeon.
- Check for other cases done on the same day.
- Whether instruments used for the surgery in question were sterilised in the same cycle.
- Verification of all steriliser indicators on the particular day.
- Relevant patient history—whether diabetic and, if so, if glycaemic status was under control.
- If more than one infection, did the same scrub nurse and doctor operate on all the cases?
- Whether the surgeon and scrub nurse scrubbed between the cases.

Thus, a multidisciplinary process from the point of early identification and prompt treatment is also necessary to determine what constitutes an outbreak and investigate the cause of the outbreak.

Outcomes

Cluster endophthalmitis cases have been reported to have a poorer visual outcome. In a report by Eifrig et al. [18], sixty-four percent of the eyes with *P. aeruginosa* were enucleated or eviscerated, and no eye achieved a visual acuity of 5/200 or better. However, in the systematic review by Pathengay et al. [10], more than 50% of the patients had a visual acuity outcome of 20/400 or better and so also in some other reports [8, 11]. Therefore, a prompt response, early identification of the outbreak and subsequent recommendations and changes in practice will ensure better outcomes and will also help in preventing future outbreaks.

Annexure 1

Campus Name:
Endophthalmitis/*SSI* Reporting Form—Form 1
(To be filled in by the primary surgeon)

Occurrence date & time: **Reporting date & time:**

Patient Data:

Name: MR #:
Type of care: Ambulatory/in-patient Age & gender:
Surgery date:
Surgical team: Surgeon:
Assistant:
Scrub Nurse:
Anesthesiologist:

Surgery Data:

Type of surgery (cataract/glaucoma/retina/others)

Date of surgery:

OR number: Sequence:
Batch number of irrigating solution:
IOL type & batch number: Type of viscoelastic used:
Duration of surgery: Start time: End time:
Postsurgical/intraoperative complication (P/C Rent/Ant Vit./*SSI*, etc.):

If Yes any prophylaxis given:

Clinical Presentation:

Duration of presentation:
Symptoms: Decrease in vision: Yes/no Pain: Yes/no
Watering: Yes/no Redness: Yes/no
Lid swelling: Yes/no
Any other details:

Visual Acuity:

IOP:
Signs (grade each sign on the scale of 1–4): Lid swelling:
Conjunctival hyperemia: Wound dehiscence/infiltration:
Corneal infiltration: AC inflammation (flare & cells):
AC hypopyon: Pupil (including exudates):
Vitreous inflammation: Retinal details:
SSI: (Specify) *Any other details:*

Final impression: Infection/inflammation/*SSI*
If infective: Bacterial or fungal

Photo documentation: Yes/no **Date** **ID**:
Management advised: (To be filled by Surgeon & the Retina/***Cornea*** Consultant)
(Include topical, systemic medication & surgical intervention)

Signature*: _____(Primary Surgeon/Assisting Surgeon/Reporting Doctor)***

Annexure 2

(Campus Name) (Place)—(Case No) (Month Year)
Endophthalmitis Case Summary

Review meeting date: ***Time:***
Venue:
Members Present:

Case History:
M.R. no:
Age:
Surgery date:
Surgery procedure:
Centre name:
Date of reporting:
Surgeon name:
MR/patient record number:

Clinical observation:

T/t recommended:

Medical treatment:
Surgery done and date:

Case review & discussion points:

A. Sterilisation recall

B. Last OR surveillance report

C. Microbiology report

D. Patient folder

Surgical recording

CCTV footage (if available)

E. Interview with primary surgeon

F. Possible predisposing factor

G. Current clinical status

H. Recommendations for improvement

Corrective action/person responsible/deadline

Signature of all members present:

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Chapter 14
Endophthalmitis After Intravitreal Injections

Raja Narayanan

Intravitreal injection is the most commonly performed procedure by retina specialists. As per reports in the USA, the number of injections performed has increased from 82,994 in 2004 to 2.5 million injections in 2011 [1].

Anti-vascular endothelial growth factor (VEGF) injections are the standard of care in neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and macular edema due to retinal vein occlusion (RVO). The commonly used agents are ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA), bevacizumab (Avastin; Genentech Inc., South San Francisco, CA), and aflibercept (Eylea; Regeneron Inc., Tarrytown, NY). The most serious vision-threatening adverse event after intravitreal injection is endophthalmitis. Bacteria can enter immediately into the vitreous cavity at the time of injection [2, 3]. Bacterial sources include the patient's ocular or periocular surfaces, aerosolized bacteria, or contamination of the needle, instruments, drug, or drug vial [4]. The rate of endophthalmitis after intravitreal injection is low, with reports in the literature ranging from 0.01% to 0.08% [5–7]. A recent meta-analysis of 43 published articles reported an overall incidence of endophthalmitis following anti-VEGF injection at 0.056% [8]. The most commonly isolated organisms were coagulase-negative *Staphylococcus* (Fig. 14.1) and *Streptococcus* species.

In spite of the extensive use of injections, evidence on relative safety with regards to endophthalmitis risk is limited. Rayess et al. studied 183 cases of endophthalmitis from approximately 500,000 anti-VEGF injections (overall rate of 0.036%) [9]. The rates of endophthalmitis were 0.039% in bevacizumab group, 0.035% in ranibizumab group, and 0.035% in aflibercept group (Table 14.1). These differences were not significant. Coagulase-negative *Staphylococcus* and *Streptococcus* species were the commonly isolated organisms in all three groups (Table 14.1). Overall, visual outcomes were better in culture-negative than culture-positive cases at 3 months

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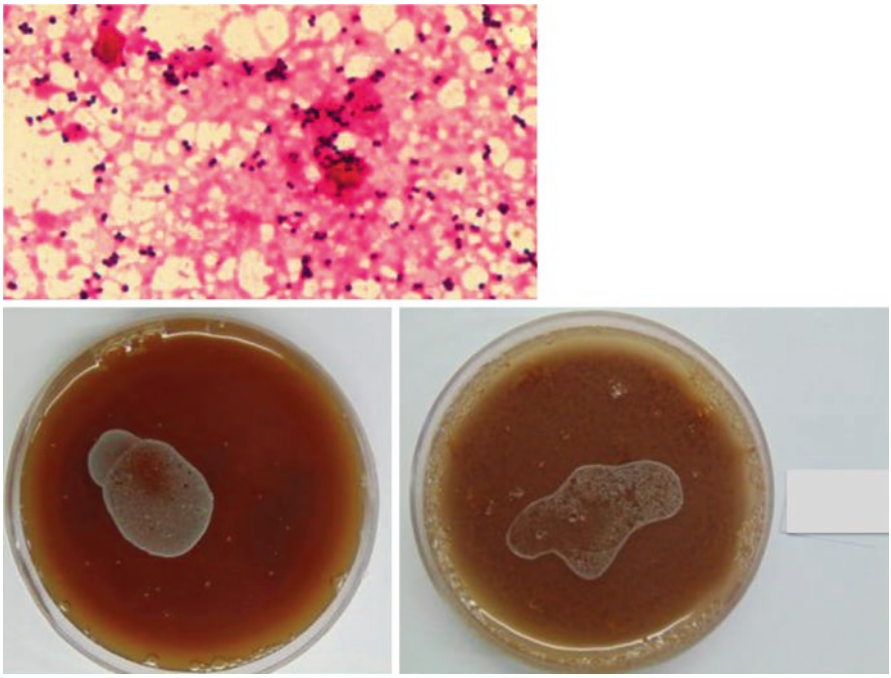

Fig. 14.1 *S. epidermidis* growth in a patient after intravitreal injection of Avastin. (*Top*) Gram stain at 100× magnification showing gram-positive cocci in groups; (*bottom*) blood (*left*) and chocolate (*right*) agar showing moist colonies without hemolysis (courtesy: Joveeta Joseph, Ph.D.)

Table 14.1 Occurrence of endophthalmitis with bevacizumab, ranibizumab, and aflibercept [9]

Molecule	Total injections	Endophthalmitis n	Rate	Common organisms
Bevacizumab	153,812	60	0.039%	*Staphylococcus* (69.6%) *Streptococcus* (21.7%)
Ranibizumab	309,722	109	0.035%	*Staphylococcus* (43.9%) *Streptococcus* (22%)
Aflibercept	40,356	14	0.035%	*Staphylococcus* (50%) *Streptococcus* (50%)

follow-up. Furthermore, culture-positive cases due to coagulase-negative *Staphylococcus* had better visual outcomes at 3 months than those related to *Streptococcus* species for all groups.

Endophthalmitis was reported after a mean of approximately 4 days from the day of injection. Mean logMAR visual acuity was 0.74 ± 0.54 (Snellen equivalent: 20/110) before the injection (baseline) and decreased to logMAR 2.27 ± 0.86 (Snellen equivalent: counting fingers, $P < 0.001$) at diagnosis of endophthalmitis. At 3 months follow-up, the visual acuity improved to logMAR 1.14 ± 1.04 (Snellen

Table 14.2 Comparison of endophthalmitis rates after anti-VEGF injection and intravitreal steroid injection [11]

Molecule	Total injections	Endophthalmitis	Rate
Anti-VEGF	387,714	73	0.019%
Steroid	18,666	24	0.13%

equivalent: 20/276, $P = 0.005$ compared to baseline vision). Although the average visual acuity improved after treatment for endophthalmitis, it was worse than the mean pre-injection visual acuity. Similar results have been shown by a study from the Bascom Palmer Eye Institute at Florida, USA [10].

The risk of endophthalmitis after an intravitreal steroid injection is much higher compared with an anti-VEGF agent injection [11]. A total of 75,249 beneficiaries in a large national US medical claims database representing 406, 380 intravitreal injections were studied. Approximately 400,000 anti-VEGF injections and 19,000 steroid injections were performed. There were 73 cases of endophthalmitis following intravitreal anti-VEGF injections (rate = 0.019% or 1 in 5283 anti-VEGF injections) and 24 cases of endophthalmitis after corticosteroid injections (rate = 0.13% or 1 in 778 steroid injections). After controlling for diagnosis, age, race, and gender, the odds ratio (OR) for occurrence of endophthalmitis was 6.92 (95% confidence interval, 3.54–13.52, $P < 0.001$) times higher post-corticosteroid injection compared with anti-VEGF injections [11] (Table 14.2).

There is a debate on whether the distribution of bevacizumab through compounding pharmacies increases the risk for endophthalmitis compared to the distribution of single-use vials of ranibizumab from the manufacturer. Vander Beek et al. reported their 8-year results (January 2005–December 2012) of intravitreal injections [12]. This analysis included 296,565 bevacizumab injections to 51,116 patients and 87,245 ranibizumab injections to 7496 patients. There were 71 cases of endophthalmitis (49 in the bevacizumab cohort and 22 in the ranibizumab cohort) for an endophthalmitis rate of 0.017% for bevacizumab and 0.025% for ranibizumab. There was no significant association with development of endophthalmitis after a bevacizumab injection compared with ranibizumab (odds ratio, 0.66 [95% CI, 0.39–1.09]; $P = 0.11$) [12].

Preoperative Prophylaxis

There are currently no randomized clinical trials evaluating the role of prophylactic topical antibiotics in this setting. Many large series have reported that topical antibiotics do not decrease the rate of endophthalmitis. This may be related to changes in the conjunctival flora due to repeated exposure to antibiotics. At this time, povidone-iodine, rather than antibiotics, is preferred for the majority of patients undergoing intravitreal injections [13].

Location of Operating Room vs. Outpatient Clinic

In the 2013 American Society of Retinal Specialists (ASRS) Preferences and Trends (PAT) Survey, over 98% of USA-based specialists reported performing injections in an office setting, compared with only 47% of international specialists [14]. In Germany and other parts of Europe, more number of injections were performed in the operating room (OR) [15]. The endophthalmitis rate has been reported to be 0.12% for office-based injections compared to 0% for OR-based injections [16].

Gloves

Even though no study has been done to analyze the role of gloves, complete aseptic precautions should be taken during intravitreal injections, as is the standard for any other intraocular surgical procedure. Since the vitreous is an avascular protein-rich tissue, even minimal bacterial contamination could lead to serious infection.

Face Mask

Surgical facemask is essential to eliminate any accidental bacterial contamination of the eye from the surgeon's mouth or nasopharynx [17]. Facemask should be even worn by those assisting in the injection procedure. As per the 2013 ASRS PAT survey, 14% of ophthalmologists reported wearing a mask during intravitreal injections [14]. In a meta-analysis of over 100,000 injections, McCannel found that almost a third of the cases were due to *Streptococcus* species. This was threefold higher than earlier studies of endophthalmitis after cataract surgery [18]. *Streptococcus* contamination is associated with poor visual acuity and an increased likelihood of enucleation. *Streptococcus viridans* are normal commensals of the upper respiratory tract and oral cavity [18, 19]. Since they are uncommonly found as part of the normal conjunctival flora, the contamination could occur from aerosolization [7, 18].

A mask may also offer protection in the event of an inadvertent cough or sneeze. The needle should remain capped until immediately before the injection [5]. Patients should be instructed to minimize talking before or during the procedure.

Povidone-Iodine

Povidone-iodine is a complex of iodide and polyvinylpyrrolidone (PVP), which acts as a reservoir of "free" iodine, and is the active component [20, 21]. The iodine penetrates cell membranes and inactivates intracellular proteins, fatty acids, and

nucleotides. It has broad-spectrum antimicrobial activity with negligible bacterial resistance. A recent survey found that over 99% of retinal specialists use povidone-iodine before intraocular injections [22].

In a randomized study, 5% povidone-iodine instilled into the conjunctival sac prior to ophthalmic surgery reduced the number of bacterial colonies by 91%, compared to a 33% reduction in control eyes [23]. In an open-label nonrandomized trial, Speaker and Menikoff found that the incidence of culture-positive endophthalmitis was 0.06% using 5% povidone-iodine, compared to 0.24% using silver protein solution [24]. In contrast, using a 2-min contact time, Ferguson et al. [25] found that 5% povidone-iodine was more effective than 1% povidone-iodine at reducing the number of colony-forming units, particularly in the presence of a heavier initial bacterial load.

Antibiotics

In the ASRS PAT Surveys, the percentage of respondents using pre-injection topical antibiotics has reduced from 40% in 2008 to 27% in 2011. The percentage using postinjection topical antibiotic has also reduced from 86% in 2008 to 62% in 2011. In 2013, 78% of US respondents indicated no use of pre- or postinjection topical antibiotics.

Pre-injection Antibiotics

No studies have shown any substantial benefit of pre-injection topical antibiotics to reduce the risk of endophthalmitis. Using antibiotics just 1–2 h preoperatively conferred no additional benefit over povidone-iodine alone in two studies [26, 27].

Antibiotics have been used post injection in several series without affecting the endophthalmitis rate [28–30]. In fact, a nonstatistically significant higher rate of endophthalmitis has been found in patients receiving postinjection antibiotics in a number of studies [31–34]. Coagulase-negative *Staphylococcus* endophthalmitis isolates resistant to fluoroquinolones at Bascom Palmer Eye Institute increased from 0% to 60.5% in 1990–2011 [34–36]. It is suspected that the widespread use of fluoroquinolones is responsible for the increasing resistance.

The LVPEI Experience [30]

We reported endophthalmitis in 8 of 15,925 anti-VEGF injections (0.05%), and this included four cases occurring in a cluster infection. All injections were given in minor theater exclusively for intravitreal injections. Seven of eight vitreous biopsies

grew coagulase-negative *Staphylococci* (CONS); this included four cluster cases growing *Staphylococcus hominis*, and one vitreous biopsy grew *Staphylococcus sanguinis*. Following vitrectomy and intravitreal antibiotic injection, four of eight patients recovered to 20/200 visual acuity at least. Repeat vitrectomy and intravitreal antibiotics were required in five patients.

It is critically important to avoid contaminating the needle with the eyelashes or lid margins before or during entry into the globe, as direct inoculation is considered to be the major mechanism by which endophthalmitis occurs [37].

A closed-blade speculum is superior to an open-blade speculum as it covers the eyelashes more effectively. In the VISION study, the most common reason for endophthalmitis was the failure to use an eyelid speculum [37]. It has been recommended that povidone-iodine should be instilled again after speculum insertion.

Conclusion

Intravitreal injection is already a standard of care in variety of retinal diseases. It is also a fact that in more common causes, such as in AMD, diabetic retinopathy, and other retinal vascular conditions, more than one injection is needed and has to be given for a longer duration of time, sometimes up to 1 year. Additionally, these injections are given to patients who are either old (AMD) or otherwise compromised due to diabetes mellitus and hypertension. Hence it is imperative that enough care is taken to prevent infection. In addition to maintaining absolute sterility during the process, there is conclusive evidence only for perioperative use of povidone-iodine and not for topical antibiotic either before or after the intravitreal injection.

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Chapter 15
Post-Vitrectomy Endophthalmitis

Vivek P. Dave

The incidence of postoperative endophthalmitis varies widely with the surgical procedure. The most widely reported series in endophthalmitis across the world includes post-cataract surgery endophthalmitis. Endophthalmitis following pars plana vitrectomy (PPV) is a relatively uncommon cause of endophthalmitis [1]. Over the last few decades, various studies have reported the incidences of post-PPV endophthalmitis; it varies from 0.03–0.14% for 20G PPV [2–11] (Table 15.1). The first reported case of endophthalmitis following sutureless PPV was in 2005 [12]. Ever since many small case series have reported endophthalmitis in small-gauge sutureless surgeries [10, 11, 13–19] (Table 15.2).

Predisposing Factors

Inadequate wound closure and subsequent hypotony were proposed as a possible risk factor in the first study reporting endophthalmitis following sutureless vitrectomy [12]. The sclerotomy leakage and hypotony would allow ingress of microorganisms from the ocular surface into the eye. Studies conducted on port site dynamics have shown that there is a definite risk of ingress of material from the ocular surface into the eye in sutureless ports as compared to those that have been sutured [19–22].

Endoscopic evaluation of autopsied vitrectomized eyes has shown that vitreous is often incarcerated at the port sites [23, 24]. This incarcerated vitreous can prolapse out of the wound and rest in the sub-conjunctival space especially following sutureless PPV. The microorganisms can potentially migrate along the vitreous blob into the intraocular space predisposing the eye to endophthalmitis.

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Table 15.1 Incidence of endophthalmitis following pars plana vitrectomy in 20-gauge surgery

Authors	Year	Case occurrence	Incidence
Ho and Tolentino [2]	1984	4/2817	0.14%
Cohen et al. [4]	1995	18/12,216	0.15%
Aaberg et al. [3]	1998	3/6557	0.04%
Zhang et al. [5]	2003	3/7000	0.04%
Eifrig et al. [6]	2004	6/15,326	0.03%
Sakamoto et al. [7]	2004	1/1886	0.05%
Joondeph et al. [8]	2005	5/10,397	0.04%
Mollan et al. [9]	2009	2/5278	0.03%
Chen et al. [10]	2009	1/3046	0.03%
Scott et al. [11]	2011	1/4403	0.02%

Table 15.2 Incidence of endophthalmitis in transconjunctival sutureless vitrectomies [10, 11, 13–18]

Authors	Year	Case occurrence	Incidence
Shaikh et al. [14]	2007	2/129	1.55%
Kunimoto and Kaiser [13]	2007	1/443	0.22%
Scott et al. [15]	2008	1/119	0.84%
Shimada et al. [16]	2008	1/3343	0.03%
Chen et al. [10]	2009	1/431	0.23%
Hu et al. [17]	2009	1/1424	0.07%
Scott et al. [11]	2011	2/4151	0.04%
Mutoh et al. [18]	2012	4/502	0.79%

The type of intraocular tamponade can also have a bearing on the risk of endophthalmitis. This is because of differential surface tension properties. As silicone oil or gas has a greater surface tension than water, both oil and gas are better tamponading agents than balanced salt solution (BSS). The risk of wound leakage is thus lesser when the tamponading agent is either gas or oil as against BSS. In a retrospective series, we have shown that the odds of post-vitrectomy endophthalmitis is 8.2 when the final tamponading agent is BSS as opposed to oil or gas [25].

Vitreous contamination by microorganisms has also been proposed as a risk factor for endophthalmitis. It has been shown that the vitreous contamination is significantly higher in sutureless transconjunctival PPV as compared to 20G PPV [26, 27]. The lesser risk of the instrument contamination in 20G surgeries was attributed to a lesser contact of the 20G instruments with the conjunctival surface. Surgeon learning curve can also increase the risk of endophthalmitis, particularly at the transition phase of the surgeon from sutured to sutureless PPV [28].

Clinical Features

The clinical features in post-PPV endophthalmitis are very similar to those seen in post-cataract surgery endophthalmitis. Most presentations are very acute with patients largely presenting within 48 h of the surgery with pain, redness, watering, and decreased vision. In the largest cohort of these cases, we have shown that the median time interval between vitreous surgery and the onset of endophthalmitis is 1.5 days [25]. Most cases do not have a favorable final visual outcome due to the underlying primary retinal disease.

Microbiology

The overall culture positivity in post-PPV endophthalmitis has been quite varied over the years. Nearly 50% of cultures across studies are culture positive. The commonest organism is coagulase-negative *Staphylococci* [29–33] (Table 15.3).

Table 15.3 Culture positivity rates in endophthalmitis after pars plana vitrectomy [4–6, 8–11, 15, 16, 18, 25, 29]

Author	Year	Culture positivity rate	Number of culture positive cases	Predominant organism
Cohen et al. [4]	1995	89%	16/18	CNS
Aaberg et al. [5]	1998	100%	3/3	CNS
Eifrig et al. [6]	2004	83%	5/6	*Staphylococcus aureus*
Joondeph et al. [8]	2005	100%	5/5	CNS
Abi-Ayad et al. [29]	2007	29%	4/14	CNS
Scott et al. [15]	2008	100%	1/1	CNS
Shimada et al. [16]	2008	100%	2/2	MRSA, *E. faecalis*
Chen et al. [10]	2009	50%	1/2	*Staphylococcus aureus*
Mollan et al. [9]	2009	0%	–	None
Scott et al. [11]	2011	50%	2/3	Coagulase-negative *Staphylococci*
Mutoh et al. [18]	2012	0%	–	None
Dave et al. [25]	2016	60%	12/20	*Staphylococcus* spp. (5) *A. baumannii* (3)

Management

The management principles remain similar to post-cataract surgery endophthalmitis except a few pointers specific to the particular clinical scenario of post-vitrectomy. During sutureless surgeries, it is recommended that the conjunctiva be displaced before making the trocar entry and be released subsequently after entry. This ensures that the conjunctival and the scleral entry wounds are not in the same line. This may reduce the access of ocular surface flora to the interior of the eyeball. An oblique entry of the trocars into the eye ensures that the wound edges do not gape further, preventing bacterial contamination by an adequate wound closure and port site leakage.

Though the endophthalmitis vitrectomy study (EVS) did not include any cases of this subgroup, the general principles of the same apply [34]. A patient suspected with post-PPV endophthalmitis should receive broad-spectrum empirical intravitreal antibiotics (vancomycin + ceftazidime/amikacin). In case of a fluid-/gas-filled eye, a lavage can be done to wash off the vitreous cavity, and the vitreous wash fluid must be sent for microbiologic evaluation. In case of a silicone oil-filled eye, only aqueous is available for evaluation. Hence AC tap should be taken for the same. Overall the visual outcome is poor (Table 15.4). Additionally, only one-fourth dose of intravitreal antibiotics and dexamethasone is injected in silicone oil-filled eyes for endophthalmitis because of the very little fluid space in such eyes.

Table 15.4 Visual acuity outcomes in reported series of post-pars plana vitrectomy endophthalmitis after treatment [4–6, 8–11, 14–16, 18, 25]

Author	Diagnosis at time of PPV	Year	Number of cases	Visual outcome at last visit
Cohen et al. [4]	ERM, MH, PDR	1995	18/12,216	Three—eviscerated Six—NLP One—LP One—HM Two—20/400 One each 20/50, 20/30, 20/25, Two—20/20
Aaberg et al. [5]	–	1998	3/6557	All eyes NLP
Eifrig et al. [6]	PDR, ERM, Recurrent RD	2004	6/15,326	Three—NLP One—LP, One—2/200, One—20/200
Joondeph et al. [8]	VH, MH, ERM, RD	2005	5/10,397	Two—NLP One—HM One—20/200 One—20/50
Shaikh et al. [14]	ERM	2007	2/129	One—20/400 One—20/40

Table 15.4 (continued)

Author	Diagnosis at time of PPV	Year	Number of cases	Visual outcome at last visit
Scott et al. [15]	ERM, PDR, CRVO, disk pit	2008	13/7682	One—LP One—HM One—20/400 One—5/200 Two—20/150 One—20/100 Two—20/20 Two—20/40, Two—20/30
Shimada et al. [16]	ERM	2008	2/6935	Both cases NLP
Chen et al. [10]	VH, TRD with VH	2009	2/3477	One—20/200 One—20/125
Mollan et al. [9]	MH, PDR	2009	2/5278	One—1/60, One—6/12
Scott et al. [11]	RD, MH, ERM	2011	3/8554	One—HM One—20/100 One—20/40
Mutoh et al. [18]	CME, ERM	2012	4/502	One—20/30 One—20/100 One—20/20 One—20/25
Dave et al. [25]	VH, TRD, RD, dropped lens, SF IOL	2016	12/38,591	Six—20/60–20/200 Six eyes—<2/200 Eight eyes—LP–no LP

CME cystoid macular edema, *CRVO* central retinal vein occlusion, *ERM* epiretinal membrane, *EV* eviscerated, *HM* hand motion vision, *LP* light perception, *MH* macular hole, *NLP* no light perception, *PDR* proliferative diabetic retinopathy, *SF IOL* secondary intraocular lens (that also needed vitrectomy), *RD* retinal detachment, *TRD* tractional retinal detachment, *VH* vitreous hemorrhage

Endophthalmitis after PPV is thus a rare but potentially very serious event. The outcomes are often poor despite prompt and appropriate treatment. The risk was potentially higher in the initial years of sutureless surgeries, which could be due less efficient scleral incision site closure. But the most recent studies have reported very low rates.

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Chapter 16
Post-Keratoplasty and Corneal Refractive Surgery Endophthalmitis

Prafulla K. Maharana, Ruchita Falera, and Namrata Sharma

Endophthalmitis is one of the most dreaded complications of ocular surgery. Keratoplasty and refractive surgeries compromise the inherent protective barrier of the eye, thereby making it prone to infections. In this chapter we review the incidence, risk factors, etiology and clinical presentation of endophthalmitis in these special cases. We will also discuss the management protocol of such cases with special emphasis on modalities to prevent such an eventuality.

Post-Keratoplasty Endophthalmitis

Infectious endophthalmitis following penetrating keratoplasty (PKP), though rare, is a devastating complication leading to poor graft survival and severe visual loss; the incidence ranges from 0.08 to 0.77% [1–6]. A downward trend has been noted over the last few decades from 0.376% during the 1980s to 0.2% in the 2000s [6]. Endophthalmitis may be either acute (within 6 weeks) or delayed in onset.

Risk Factors

A number of factors have been associated with development of endophthalmitis in post-keratoplasty patients. They include the donor cornea from persons dyeing from infection [7]; culture-positive donor tissues [8]; high risk indications, such as injury, infection, ulcerative keratitis and impending or actual corneal perforation; and

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history of previous ocular surgery. Postoperative events like suture removal, wound dehiscence and vitreous incarceration are other factors associated with the development of endophthalmitis.

Etiology

Both bacteria and fungi have been the cause of post-keratoplasty endophthalmitis. In a study conducted by Kunimoto et al. [9], Gram-positive cocci were the most common aetiologic pathogen isolated in about 76.9% cases. Of these, *Streptococcus* species were more common, accounting for about 50% of all cases of endophthalmitis. Others included *Staphylococcus* species as well as Gram-negative bacteria like *Proteus mirabilis* and *Serratia marcescens*. Fungi are an important cause of post-keratoplasty endophthalmitis. *Candida* species (especially *C. albicans*) is responsible for almost 90% of post-keratoplasty fungal endophthalmitis and accounts for approximately 15–20% of all post-keratoplasty endophthalmitis [10]. *Cladosporium*, *Cryptococcus* and *Aspergillus* species are other rare causative pathogens [11, 12].

Kunimoto et al. [9] noted a higher culture positivity at 92.9% in post-keratoplasty endophthalmitis; this is significantly higher compared to post-cataract surgery endophthalmitis. Higher bacterial load, greater virulence of the pathogens, donor cornea as source of infection and the use of higher potency corticosteroids for longer period of time could be contributing factors.

The source of infection in cases of post-keratoplasty endophthalmitis may be varied, ranging from donor tissue contamination to contamination from host ocular flora. Preoperative corneal button contamination is the most common source of infection. In a report by the Eye Bank Association of America, 1991–1994, concordant-positive donor and recipient cultures were confirmed in 53% case [13]. Others have published positive donor corneal rim culture between 56% and 76% [1, 10, 14]. Contamination could occur at preliminary stages, like inadequate asepsis during retrieval of the corneal tissue or processing and storage of the corneal tissue. The lack of aseptic measures during surgery and postoperative wound leak could further predispose to the development of postoperative endophthalmitis [3]. Patients' ocular flora can be a potential source of contamination as documented by Speaker et al. in post-cataract surgery endophthalmitis [15]. Delayed-onset endophthalmitis could be associated with suture abscess or bacterial entry into the eye through the area of corneal thinning or loose sutures [16].

Clinical Features

Endophthalmitis following keratoplasty could occur within 6 weeks (acute-onset endophthalmitis) or later than 6 weeks (delayed-onset endophthalmitis). Unlike post-cataract surgery endophthalmitis, the disease may be relatively painless at the onset [17]. Visual acuity is less than expected, which may even be hand motions or perception of light. On examination, the graft appears oedematous with decreased

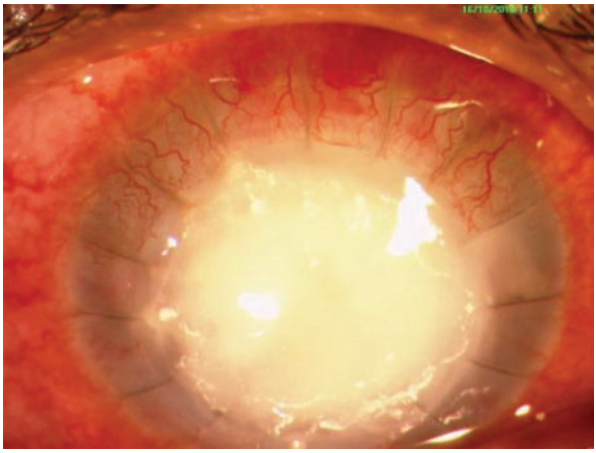

Fig. 16.1 Post-penetrating keratoplasty graft infection with endophthalmitis

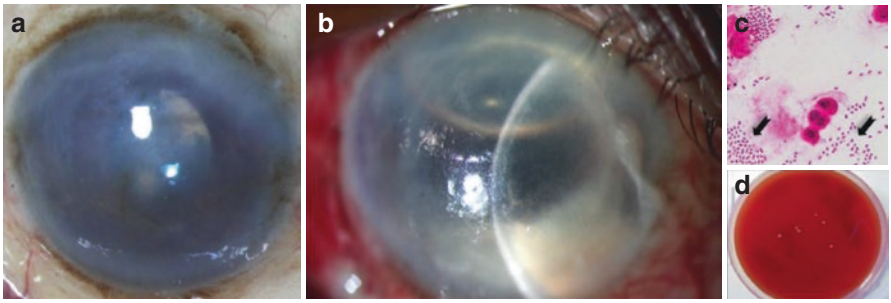

Fig. 16.2 Post-DSEK endophthalmitis. (**a**) A case of pseudophakic corneal oedema that received DSEK. (**b**) Post-DSEK acute endophthalmitis with infiltrates in donor lenticule and anterior chamber. (**c**) Gram-negative coccobacilli (*arrows*) seen in smears (Gram stain, 100×). (**d**) Blood agar showed white mucoid colonies (*centre*) of *Klebsiella pneumoniae* (Courtesy: Shilpa Das, MD)

clarity. Severe anterior chamber reaction, hypopyon and loss of red glow are the common features. In late-onset cases, suture infiltrates, suture abscess and epithelial defect with surrounding infiltrates may also be seen (Figs. 16.1 and 16.2). Fungal endophthalmitis may additionally present with white fluffy material in the anterior chamber or endothelial plaques. In a case of endophthalmitis due to *Aspergillus flavus*, the disease may initially present as an extension from the graft-host junction without the presence of any significant stromal keratitis, endothelial plaque or anterior chamber reaction [18].

Differential Diagnosis

A number of conditions mimic endophthalmitis. An acute episode of graft rejection is the most common condition confused with a case of endophthalmitis. A case of acute rejection would present with sudden graft oedema, with reduction of vision, epithelial and endothelial rejection line, the presence of keratic precipitates and

possible raised intraocular pressure. The absence of infiltrates on the donor cornea, presence of red reflex and rapid resolution in response to steroid differentiate a graft rejection from endophthalmitis.

A recurrent corneal herpetic infection is another entity which can be confused with post-penetrating keratoplasty endophthalmitis. A history of previous episodes of redness and pain, affliction of both donor and host cornea and prompt response to antiviral therapy differentiate a herpetic corneal infection from post-keratoplasty endophthalmitis.

Investigations

Every clinically diagnosed case of endophthalmitis should be confirmed by culturing the organisms from the intraocular samples. The area of the donor tissue with infiltrates should be scrapped for microscopy and culture. At least two smears are prepared, one for Gram staining and the other for potassium hydroxide (KOH) wet mount. Further, the scrapping should be directly inoculated into the culture media, and sensitivity of the organism to the antibiotics should be obtained. The corneal samples are routinely inoculated onto blood agar plate and Sabouraud's dextrose agar, when fungus is suspected. If a suture abscess or infected suture tract is present, the removed suture must be cultured. B-scan ultrasonography should be done to look for mild to moderate spikes in vitreous cavity suggestive of exudates. The most important samples to be cultured are aspirates from the aqueous and vitreous cavity. Vitreous biopsy taken and cultured in such cases may serve as a useful guide to the treatment.

Prevention

Since the treatment outcome in endophthalmitis after penetrating keratoplasty is poor, prevention of such infection is more important. The donor cornea is one of the important factors responsible for endophthalmitis; hence all measures must be taken to reduce contamination of the tissue at donor screening, and strict asepsis must be maintained during tissue harvesting. Povidone-iodine is known to have antibacterial and antifungal action. Instillation of povidone-iodine 2.5% in the conjunctival cul-de-sac prior to retrieval of donor tissue significantly reduces microbial load of the donor cornea [19]. Contaminated tissue storage media are a potential source of infection. A change in the colour of the medium from pink to yellow indicates a change in pH and possible microbial contamination. Hence no donor tissue from such storage medium should be used for transplantation. The incidence of fungal endophthalmitis is less with organ-cultured corneas. This is mainly because of amphotericin B added to the organ culture media as well as microbiological screening which is routinely performed before using the tissue.

Management

Endophthalmitis is an infrequent but serious intraocular infection. A high level of suspicion helps, as timely intervention is the key to control the disease. Gram-positive organisms accounted for nearly half of all cases of endophthalmitis in one study; they exhibited 100% susceptibility to vancomycin, bacitracin and ampicillin, and only 75% of Gram-positive cocci were sensitive to cefazolin [9]. Gram-negative bacteria showed sensitivity to both ceftazidime and gentamicin [9]. *Candida albicans* is the most common infecting fungus. Topical antifungal medications are generally unstable and have poor corneal penetration [20]; according to the Infectious Diseases Society of America (IDSA) guidelines [21], intravenous voriconazole at a dosage of 3–4 mg/kg twice daily is safe and achieves excellent intravitreal levels for *Candida* endophthalmitis [22].

Unlike post-cataract surgery endophthalmitis, no study has shown a preferred route of antibiotic delivery in the treatment of post-penetrating keratoplasty endophthalmitis. According to the current microbiologic spectrum and susceptibilities, empiric antibiotic treatment should include vancomycin for Gram-positive bacteria and ceftazidime or amikacin for Gram-negative bacteria. Amphotericin B or voriconazole may be added in a case suspected of fungal endophthalmitis.

The mainstay of treatment of post-penetrating keratoplasty endophthalmitis is management of graft infection. Intravitreal antibiotics may have to be administered in a majority of cases. However, the integrity of the graft-host junction should be secured before intravitreal injection of drug. Pars plana vitrectomy using a temporary keratoplasty followed by repeat graft could be a viable option in fulminant cases.

Outcome

The outcome of post-penetrating keratoplasty endophthalmitis is dismal. As reported by Chen et al. [7], 5-year graft survival was only 27% after the development of endophthalmitis and the mean logMAR best corrected visual acuity in the surviving grafts was 1.13 (Snellen equivalent 20/269). In a review of *Candida* endophthalmitis after keratoplasty, 60% of cases resulted in visual acuity of 20/200 or worse [10].

Post-Refractive Surgery Endophthalmitis

Refractive error is the most common cause of ocular morbidity in the world. With improving technology and increased experience among ophthalmologists, there has been a tremendous increase in the number of people undergoing refractive surgeries. The realm of refractive surgery in vast majority includes incisional surgeries like radial keratectomy, ablative laser procedures like photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) and intraocular surgeries like

phakic IOL implantation and refractive lens exchange. Since ablative laser procedures are primarily extraocular, the incidence of endophthalmitis in these cases is rather low with a few cases reported in literature. Intraocular surgeries like implantable collamer lens (ICL) have a considerable risk of endophthalmitis with a reported incidence of 1 in 6000, i.e. 0.0167% [23].

Risk Factors and Source

Patients at an increased risk of developing a persistent epithelial defect (e.g. corneal hypaesthesia, limbal stem cell deficiency and dry eye syndrome) are predisposed to the development of infection [24]. Patients should therefore be carefully assessed and counselled regarding these risks prior to surgery. The presence of corneal epithelial defect significantly increases the risk of infection. This is more in cases of PRK as compared to LASIK although small epithelial defects may be present with the latter as well. The use of bandage contact lens after PRK is a common practice. Although it may reduce pain and aid rapid re-epithelization, the risk of microbial keratitis is increased. Reduced corneal sensitivity which may persist for weeks after PRK may also be a contributing factor to infections [25]. The use of corticosteroids postoperatively further renders the eye susceptible to infections [26]. In post-LASIK eyes, the protection offered by the normal corneal epithelium and Bowman's membrane is compromised, and the thinned cornea further increases the accessibility of the infective organism into the eye. There is also a higher chance of contamination of the interface with the patient's own conjunctival secretions which is a potential source of infection. The use of microkeratome has an increased risk of infection compared to femtosecond laser-assisted LASIK surgeries. The incidence of fulminant infections is more in eyes with prior refractive surgeries, such as radial keratotomy (RK) before LASIK or PRK procedures [27–30].

Etiology

Endophthalmitis post-refractive surgery is a rare entity. Mulhern et al. [31] reported a case of *Streptococcus pneumoniae* endophthalmitis following an uneventful astigmatic myopic LASIK correction. A case of postsurgical endophthalmitis following PRK in a patient with a remote history of RK was reported by Karth et al. [30]; the causative organism was methicillin-resistant *Staphylococcus aureus*. In an anonymous online survey across 21 countries between January 1998 and December 2006, three cases of endophthalmitis were reported, and *Staphylococcus epidermidis* was cultured in two of them [23]. There have been reported cases of endophthalmitis following refractive lens procedures caused by *Fusarium*, *Pseudomonas aeruginosa* and *Aspergillus* [32–34]. There are also case reports of late-onset *Mycobacterium gordonae* endophthalmitis following anterior chamber phakic intraocular lens (PIOL) implantation for high myopia [35], *Streptococcus mitis/oralis* endophthalmitis after

complicated iris-fixated PIOL implantation [36], methicillin-resistant *Staphylococcus epidermidis* endophthalmitis following uncomplicated posterior chamber PIOL implantation [37] and *Rhizobium radiobacter* endophthalmitis after posterior chamber PIOL implantation for myopia 25 months after the primary surgery [38].

Clinical Features

The onset of symptoms is classified as 'early', if it occurs within 7 days of refractive surgery, and 'late' if it occurs 10 days or more after the last surgical intervention. The most prominent symptom is sudden diminution of vision. The patients may present with associated pain, photophobia and discharge.

In cases of endophthalmitis following LASIK, slit lamp examination could reveal epithelial defect with surrounding infiltrates. Flap oedema is present in a majority of cases. Stromal abscess with severe anterior chamber reaction is seen in many cases (Figs. 16.3 and 16.4). Associated findings of epithelial ingrowth and flap separation may also be seen. Interface debris and infiltrates should be carefully looked for.

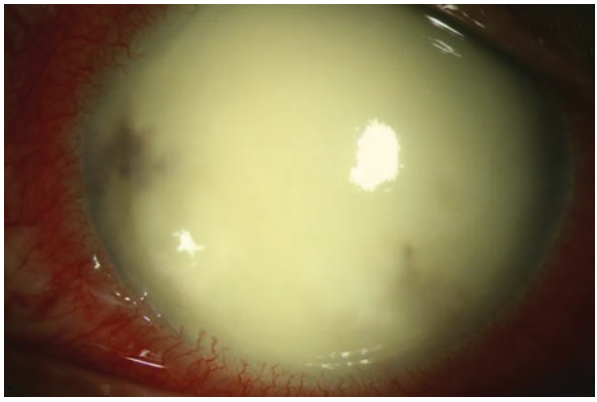

Fig. 16.3 Post-LASIK infection with stromal abscess with anterior chamber exudates

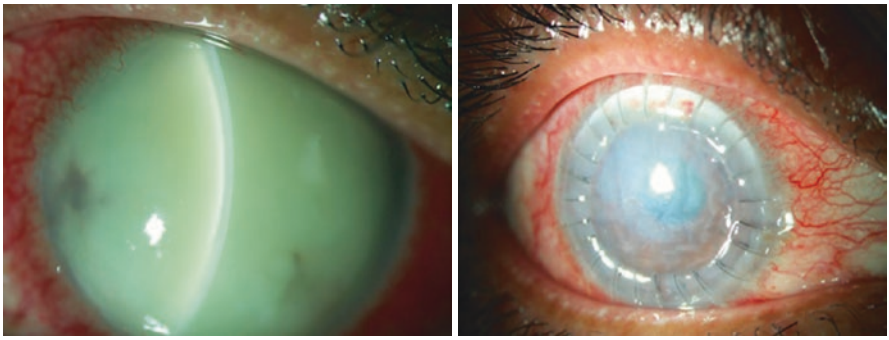

Fig. 16.4 (*Left*) Post-LASIK keratitis with endophthalmitis; (*right*) following therapeutic graft

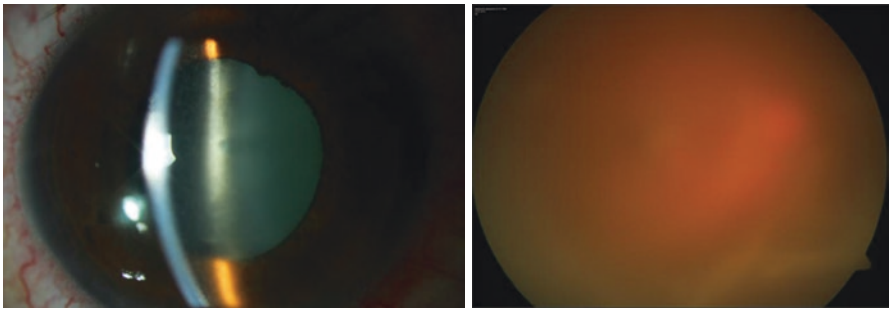

Fig. 16.5 Post-ICL endophthalmitis. (*Left*) With anterior chamber 4+ cells; (*right*) with vitreous haze. (Courtesy: ShilpSa Das, MD)

Cases of post phakic IOL endophthalmitis (Fig. 16.5) present similar to that following routine cataract surgery.

Differential Diagnosis

Endophthalmitis following LASIK or PRK is generally preceded by infectious keratitis. Any such infection should be promptly diagnosed and treated in order to avoid such eventuality. The closest differential of infectious keratitis in a case of prior LASIK procedure is diffuse lamellar keratitis (DLK) which is a non-infectious postoperative inflammation. It is important to differentiate the two entities. DLK needs an aggressive treatment with corticosteroids, whereas corticosteroid treatment could worsen an infection. DLK typically presents with interface inflammation without infiltrates, 1–5 days after surgery. Slit lamp biomicroscopy in DLK demonstrates peripherally located wavy white lines of inflammatory cells, classically described as ‘Sands of Sahara’. In contrast, post-LASIK infectious keratitis usually begins 2–3 days after surgery. The inflammatory reaction is not confined to the interface alone but can extend up into the flap, deeper into the stromal bed or even into the anterior chamber.

Investigations

A suspected case of post-refractive surgery infection should be promptly investigated to make a confirmatory diagnosis. Any associated corneal ulcer with infiltrates should be promptly scrapped. Because a corneal scraping may result in loss of the flap, other means of obtaining sample for culture like anterior chamber tap could be considered. Smears prepared from the sample should be subjected to Gram staining and KOH wet mount. Direct inoculation into the culture media and antibiotic sensitivity of the organism should be obtained. B-scan ultrasonography

showing the presence of multiple mild to moderate amplitude echoes in the vitreous cavity, suggestive of vitreous exudates, confirms the diagnosis of endophthalmitis. A vitreous tap should be performed and the aspirate sent for culture sensitivity in all cases.

Management

Endophthalmitis in cases following refractive surgery are a relatively rare occurrence with varied aetiology. The treatment protocol in these cases mainly depends upon the suspicion of infection and prompt action. In a majority of these cases, the offending organisms are Gram-positive bacteria and respond to empiric therapy of intravitreal vancomycin, usually combined with ceftazidime.

Endophthalmitis following ICL implantation may be rarer than after cataract surgery. Treatment in these cases is generally guided by antibiotic sensitivity of the cultured organism from the intravitreal sample. In a majority of cases, ICL explanation is not required and visual rehabilitation is complete. In a single case report, ICL was explanted and reimplanted after successful resolution of endophthalmitis 9 months after the event; this eye regained 20/20 vision [37].

To conclude, the outcome of endophthalmitis, though a rare occurrence in today's ophthalmologic practice, could be very discouraging. All steps should be taken to prevent the occurrence of the disease. With accurate diagnosis and prompt action, favourable visual prognosis is possible.

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Chapter 17
Endophthalmitis Caused by Gram-Negative Bacteria

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Endophthalmitis caused by gram-negative bacteria is less common compared to gram-positive bacteria and generally has poor visual acuity outcomes. More common gram-negative bacteria causing endophthalmitis include species of *Pseudomonas*, *Klebsiella*, *Proteus*, *Haemophilus*, and *Enterobacter*. *Pseudomonas* and *Enterobacter* are reportedly more common. Gram-negative endophthalmitis may present with symptoms of variable pain, redness, inflammation, and decreased visual acuity. The clinical signs include eyelid edema, conjunctival chemosis/erythema, corneal edema, hypopyon, fibrinous membrane in the anterior chamber or on intraocular lens, vitritis, and periphlebitis (Fig. 17.1).

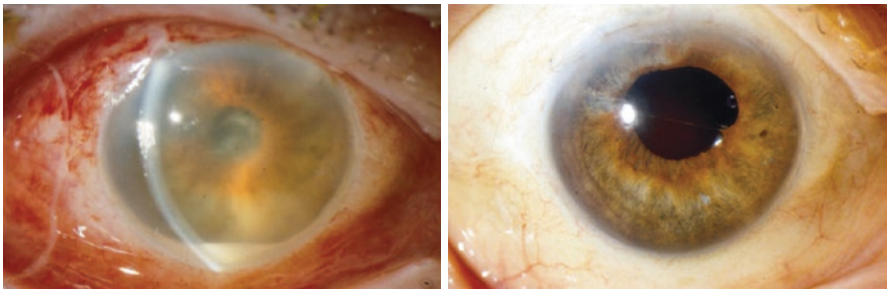

Fig. 17.1 (*Left*) Patient with postoperative endophthalmitis on day 1 after cataract surgery. Managed with pars plana vitrectomy and intravitreal antibiotics. (*Right*) Quiet eye showing resolved infection at 6-month follow-up. Vitreous grew *Serratia marcescens* and was sensitive to aminoglycosides and cephalosporins

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Table 17.1 Rates of endophthalmitis postcataract surgery caused by gram-negative bacteria [1–4]

Series	Country	Endophthalmitis rate %
EVS, 1990–1994 [1]	USA	5.9%
Jindal et al. 2013 [4]	India	26–42
Kamalarajah et al. 2004 [2]	Europe	6–12
Altan et al. 2009 [3]	Turkey	35.1

Table 17.2 Common gram-negative organisms causing endophthalmitis [1]

Common gram-negative bacteria causing endophthalmitis	
Enterobacteriaceae group	Non-*Enterobacteriaceae* group
Proteus species	*Pseudomonas* species
Serratia species	*Haemophilus* species
Achromobacter species	*Burkholderia* species
	Bacteroides species
	Neisseria species

Prevalence and Classification

The clinical settings in which endophthalmitis caused by gram-negative bacteria can occur include postoperative, post open-globe injury, and endogenous. Postoperative endophthalmitis is more common. The rate of endophthalmitis caused by gram-negative bacteria is reported to be 26–42% in developing countries and 5.9–12% in developed countries [1–4] (Table 17.1). It is important to note that gram-negative bacteria constitute <5% of the conjunctival and lid flora in adults [5]. Hence, in most cases, the organism is introduced from an exogenous source.

Gram-negative bacteria could be classified into cocci and bacilli. On the basis of biochemical profile and antibiotic resistance, gram-negative bacteria could also be classified in two groups—enterics (*Enterobacteriaceae*) and non-enterics (non-*Enterobacteriaceae*) (Table 17.2, [1]).

Enterobacteriaceae group have pathogens that are increasingly becoming multidrug resistant particularly to third-generation cephalosporins due to the overproduction of beta-lactamases. The non-*Enterobacteriaceae* group are known to be inherently resistant to many third-generation cephalosporins and fluoroquinolones.

Virulence Factors and Pathogenesis

Gram-negative bacteria have various virulence factors, which act like enzymes that dissolve tissues or toxins that kill the cells. Virulence factors include endotoxin/lipopolysaccharide (LPS), exotoxins, and enterotoxins [6]. Some virulence factors are organism specific and will be discussed along with organisms subsequently.

Endotoxin/LPS—This virulence factor is present in the outer membrane of the gram-negative bacteria. These are the glycopeptides, which make up about 75% of

outer membrane of gram-negative organisms that are capable of causing lethal shock. Lipopolysaccharide consists of a lipid-A domain, an oligosaccharide core, and the outermost O-antigen polysaccharide. Lipid-A domain is the region identified by innate immune system, and even small concentration of it is sufficient to trigger immune response that manifests in release of cytokines (interleukin-1β, tumor necrosis factor-α) from macrophages. Lipid-A component of LPS can also cause endothelial cell injury by promoting the expression of tissue factor and pro-inflammatory cytokines, leading to apoptosis of these cells. Presence of lipid-A in bloodstream can lead to endotoxin shock. LPS binds to the toll-like receptors (TLR-4) and activate it resulting in further release of inflammatory cytokines.

Exotoxin/Protein A—Exotoxin A is part of an enzyme family called mono-ADP-ribosyltransferase [6]. The toxin catalyzes the ADP ribosylation of eukaryotic elongation factor 2 and affects the protein synthesis in host cells by a mechanism similar to diphtheria toxin. This secreted exotoxin is a potent virulence factor specifically for *Pseudomonas* species.

Specific Gram-Negative Endophthalmitis

Endophthalmitis caused by the common gram-negative bacteria is discussed in this section. These bacteria have some specific toxins and virulence factors that may be associated with severe inflammation and tissue damage.

Endophthalmitis Caused by Proteus Species

Proteus species is a part of normal colonic flora and is often associated with urinary tract infections, pneumonia, otitis media, and wound infections. Endophthalmitis by *Proteus* species results from inoculation of normal flora into the eye. It could occur in the following settings: postcataract surgery, retained lens fragment during cataract surgery, penetrating keratoplasty, scleral buckle procedure, trauma, and ocular prosthesis. *Proteus* species are the most frequent gram-negative bacteria causing postoperative endophthalmitis after cataract surgery [7, 8]. In the Endophthalmitis Vitrectomy Study (EVS), *Proteus* species accounted for 6/19 (32%) cases of gram-negative bacteria among 291 cases (323 isolates) studied (Table 17.3) [1].

Infection with *Proteus* species progresses rapidly and causes extensive tissue destruction. Virulence factors such as endotoxin, hemolysin (aids in spread of infection), urease (increases tissue pH), and presence of fimbriae on surface (aid in adherence and colonization of tissues) in *Proteus* species help bacteria in tissue damage [9]. Visual prognosis is poor in most of the studies. Aminoglycosides and beta-lactam antibiotics (ceftazidime) are active against most of the *Proteus* species. The reported resistance to aminoglycosides and beta-lactam drugs is an important concern as these are the first-line intravitreal drugs used in the empiric management of endophthalmitis against gram-negative bacteria.

Table 17.3 Gram-negative organisms reported in the Endophthalmitis Vitrectomy Study [1]

Gram-negative organisms reported in the EVS (19/323 isolates from 291 patients)	
Gram-negative organisms	*n/N* (%)
Proteus mirabilis	6/19 (1.9)
Pseudomonas aeruginosa	3/19 (0.9)
Pseudomonas vesicularis	1/19 (0.3)
Pseudomonas fluorescens	1/19 (0.3)
Morganella morganii	2/19 (0.6)
Citrobacter diversus	2/19 (0.6)
Serratia marcescens	1/19 (0.3)
Enterobacter agglomerans	1/19 (0.3)
Enterobacter aerogenes	1/19 (0.3)
Flavobacterium species	1/19 (0.3)

Leng et al. reported a retrospective consecutive case series of all culture-positive endophthalmitis cases over a period of 24 years, 1983–2007 [9]. In this series, 1751 organisms were isolated from intraocular culture, and 244 were gram-negative organisms. *Proteus* species was identified in 13 cases (5%; 13/244). All the isolates in this study were susceptible to aminoglycoside antibiotics. Visual outcomes in this study were poor despite treatment with sensitive antibiotics. Visual acuity of 20/200 or worse was reported in 12 patients including 8 patients with light perception or worse. The patients who underwent early vitrectomy did better than those who were managed with initial tap and injection of antibiotics; however, due to small number of cases, no statistical conclusion could be made.

Endophthalmitis Caused by Klebsiella Species

Klebsiella is part of the normal flora of nasopharynx and gastrointestinal tract. *Klebsiella* species have emerged as a leading cause of pyogenic liver abscess in Asia. Patients with liver abscess, diabetes mellitus, immunocompromised status, delayed treatment of systemic *Klebsiella* infection, and poor glycemic control are at high risk of developing endogenous endophthalmitis. *Klebsiella* liver abscesses are associated with 3–11% incidence of endogenous endophthalmitis [10, 11]. Polysaccharide capsule (specific capsular serotypes conferring resistance to phagocytosis) and genetic susceptibility to K1 and K2 serotypes of *Klebsiella pneumoniae* act as virulence factors and help the organism evade immune response of the host with resultant infection [12]. Patients with endogenous endophthalmitis caused by *Klebsiella* species have higher rate of mortality.

Klebsiella species infection was not reported in the EVS [1]. Endophthalmitis caused by *Klebsiella* species, though hitherto less common, is increasingly reported worldwide and in the USA [13–18]. It is generally associated with poor visual outcomes despite adequate treatment. Endogenous endophthalmitis cases have higher rates of enucleation or evisceration. Some advocate early surgical intervention such as pars plana vitrectomy, in view of poor visual and anatomical outcomes.

Sridhar et al. compiled a non-comparative consecutive case series of seven patients with *Klebsiella* endophthalmitis during a period of 22 years, 1990–2012, from a large university referral center [19]. They reported that endogenous cases in this series were associated with poorest outcomes and that all cases underwent evisceration or enucleation. In another case series, three patients of multidrug-resistant *Klebsiella* species endophthalmitis ran a rapid and fulminant course with severe intraocular inflammation [20]. The organisms in this small series of three cases were susceptible only to imipenem, and despite treatment the outcome was poor.

Endophthalmitis Caused by Achromobacter Species

Achromobacter xylosoxidans is an aerobic, motile, gram-negative bacillus common in humid environment and is an important nosocomial pathogen. *Achromobacter* is the part of normal flora of ear and gastrointestinal tract. Although it is an uncommon pathogen, it could cause both acute-onset and delayed-onset postoperative endophthalmitis. *Achromobacter xylosoxidans* infection is more commonly seen in immunocompromised hosts, renal insufficiency, diabetes mellitus, carcinoma, alcoholism, tuberculosis, or endogenous immunosuppressed individuals [21, 22]. It may infect immunocompetent individuals as well. This organism has been shown to produce biofilm to survive in toxic environment [23]. It is important to differentiate between *Pseudomonas* species and *Achromobacter xylosoxidans* as both organisms are gram-negative, non-fermentative bacilli growing in humid environment and opportunistic pathogens with very similar antibiotic resistance pattern. *Pseudomonas* species are invariably associated with a fulminant and a severe disease course as compared to indolent course for *Achromobacter xylosoxidans.* A retrospective study suggested that ceftazidime and amikacin are the antibiotics of choice for ocular infections by *Achromobacter xylosoxidans* [24].

In 2014, Villegas et al. reported non-comparative consecutive case series of culture-proven *Achromobacter xylosoxidans* endophthalmitis between 1970 and 2012 at a university referral center in the USA [25]. All four patients in this series with endophthalmitis caused by *Achromobacter xylosoxidans* underwent capsulectomy, intraocular lens removal, and intravitreal injection of antibiotics at the time of pars plana vitrectomy. Two of four patients recovered to 20/40 or better, and the vision in other two patients was 20/200 or worse.

Endophthalmitis Caused by Serratia Species

Serratia marcescens is a gram-negative bacillus most often implicated as a cause of nosocomial infections such as hospital-acquired pneumonia, urinary tract infection, and wound infection [26]. In the EVS, *Serratia marcescens* was not identified in any of the culture-positive isolates [1]. The visual and anatomic outcomes are usually poor [26].

Sridhar et al. reported ten cases over 20-year period, 1993–2012, of *Serratia marcescens* endophthalmitis at a large university referral center. All isolates were sensitive to gentamicin, ceftazidime, imipenem, and levofloxacin and further reported that MIC90s of isolates for antibiotics tested remained unchanged from 1980 onward. All isolates were resistant to vancomycin. In this series, outcomes were generally poor with a high rate of complete visual loss in the affected eye. Final visual acuity was no light perception in six of ten patients.

Endophthalmitis Caused by Pseudomonas Species

In the EVS, *Pseudomonas aeruginosa* accounted for approximately 1% of culture-positive endophthalmitis cases (Table 17.3) [1]. Few other large series have reported incidence of *Pseudomonas aeruginosa* acute postoperative endophthalmitis from 8% to 34% [3, 27, 28]. *Pseudomonas aeruginosa* produces elastases and exotoxins that may cause permanent damage to the intraocular contents and cause severe globe disorganization. This bacteria can survive well in aqueous environment for long periods as multiple outbreaks of *Pseudomonas aeruginosa* endophthalmitis have been reported secondary to contaminated ophthalmic solutions, phacoemulsifier internal fluid, intraocular lens solution, and contaminated phacoprobes [29–32]. There are reports of increasing drug resistance among *Pseudomonas aeruginosa* to fluoroquinolones, aminoglycosides, piperacillin-tazobactam, and ceftazidime [4, 33]. In one case of endophthalmitis due to gram-negative bacteria resistant to aminoglycoside and cephalosporin, intravitreal imipenem helped resolution of infection [20]. Efflux pumps and inhibition of drug intake are common components of multidrug-resistant *Pseudomonas* isolates that prevent accumulation of antibacterial drugs within the bacterium [34].

Sridhar et al. reported 12 consecutive cases of *Pseudomonas aeruginosa* endophthalmitis over a 10-year period. The primary surgeries were cataract surgery, penetrating keratoplasty, pars plana vitrectomy, glaucoma filtration surgery, and endogenous infection [35]. In this series, all patients presented with hypopyon and poor visual acuity (hand motions or worse). All isolates were susceptible to ceftazidime and levofloxacin and the MIC90 remained stable as compared to isolates from 1987 to 2001. Visual and anatomical outcomes were poor in this series despite early and appropriate treatment. Visual acuity at final follow-up was 20/400 or worse in 11 of 12 patients, light perception in 8 of 12 patients, and enucleation was required in five patients.

Endophthalmitis Caused by Haemophilus Species

Haemophilus influenzae is a fastidious, aerobic, gram-negative coccobacillus, which is an uncommon cause of endophthalmitis. Endophthalmitis caused by *Haemophilus influenzae* could occur in following clinical settings: filtering surgery,

cataract surgery, strabismus surgery, vitrectomy, intraocular lens (IOL) implantation, IOL extrusion, and corneal ulceration [36–38]. Delayed onset endophthalmitis more often occurs in bleb-associated endophthalmitis caused by *Haemophilus influenzae* [39]. In the EVS, none of the cases were reported with *Haemophilus* species infection [1].

Yoder et al. reported a retrospective, non-comparative, 16 consecutive cases of *Haemophilus influenzae* endophthalmitis during 22 years at a university teaching center [39]. In this cohort, vitreous tap and intravitreal antibiotic injection was given initially in nine eyes, and a vitrectomy was performed initially in the remaining seven eyes. In addition to all eyes receiving intravitreal antibiotics at initial treatment presentation, 11 eyes also received intravitreal dexamethasone. The organisms were sensitive to at least one of the initial intravitreal antibiotics administered in all cases. The visual outcome was poor despite prompt treatment with sensitive intravitreal antibiotics. Final visual acuity was 5/200 or better in six eyes, and in six eyes, the final visual acuity was no light perception.

Antimicrobial Susceptibilities

Intravitreal ceftazidime or amikacin are commonly used drugs for the empiric treatment of gram-negative endophthalmitis. In the EVS, 89.5% of gram-negative bacteria were sensitive to both amikacin and ceftazidime. However, Kunimoto et al. reported gram-negative isolates susceptibility to ciprofloxacin (87.5%), amikacin (82.1%), and ceftazidime (60.9%) [40]. In a recent publication by the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) surveillance study in 2015, there was no increase in overall ocular resistance during the 5-year study period (January 2009–December 2013) [41]. A recent report on antimicrobial susceptibilities (measured by disk diffusion, Vitek 2, and E-test) evaluated the records from culture-positive vitreous isolates (endophthalmitis cases with gram-negative bacteria) during a 24-year period (December 1990–December 2014), at the Microbiology Department of Bascom Palmer Eye Institute, Miami, Florida, USA, for four antibiotic groups: aminoglycosides, cephalosporins, carbapenems, and fluoroquinolones (Wilson et al. submitted to JAMA Ophthalmology 2016). This report showed no increase in drug resistance. A prior 9-year (January 1982–December 1990) study from the same center also showed no increase in the drug resistance among gram-negative bacteria [36]. The collective experience from these studies shows that antibiotic susceptibility pattern of gram-negative bacteria from vitreous isolates has not changed.

Drugs such as fluoroquinolones and imipenem reportedly are highly effective against these gram-negative organisms. In a case series of endophthalmitis caused by multidrug-resistant gram-negative infection in three patients, organisms were susceptible only to imipenem [20]. But the outcome was not good in these three eyes despite treatment with intravitreal imipenem.

Mechanism of Drug Resistance—Multidrug resistance is reported to be more common in gram-negative organisms compared to gram-positive organisms [42]. Widespread use of antibiotics along with cross transfer of multidrug resistance remains an important mechanism of emerging drug resistance.

Deactivation of aminoglycosides by aminoglycoside-modifying enzymes, reduction of the intracellular concentration of aminoglycosides by changes in the outer membrane permeability which is usually a nonspecific resistance mechanism, inner membrane transport, active efflux or drug trapping, the alteration of the 30S ribosomal subunit target by mutation, and finally methylation of the aminoglycoside-binding site are the mechanisms of aminoglycoside resistance [43].

Beta-lactam antibiotics (cephalosporins) undergo enzymatic deactivation of the drug by β-lactamase produced by various gram-negative bacteria leading to drug resistance. β-lactamase inhibitors including clavulanic acid, sulbactam, and tazobactam inhibit β-lactamase and thus are given along with β-lactam drugs. *Pseudomonas* species has an additional capability of producing AmpC β-lactamase (also known as cephalosporinase) whose activity is not inhibited by β-lactamase inhibitors [44].

Diagnosis

Quick identification of organism causing endophthalmitis is important for appropriate management. Standard diagnostic methods including smear preparation for specific stains (gram stain, acid-fast stain, acridine orange, calcofluor white) and growth on selected culture media are used most commonly (chocolate agar, 5% sheep blood agar, thioglycollate broth, anaerobic blood agar, Sabouraud agar, blood culture bottles, Lowenstein-Jensen medium, CHROMagars). Newer diagnostic tests including PCR (real time, multiplex), DNA microarrays, matrix-assisted laser desorption, ionization time-of-flight mass spectrometry (MALDI-TOF), peptide nucleic acid fluorescent in situ hybridization (PNA-FISH), and next-generation sequencing help in rapid organism recovery and identification directly from patient samples and/or culture media [45].

Treatment Options

Cephalosporins and aminoglycosides are among the drugs of choice for treating endophthalmitis caused by gram-negative bacteria. In case of resistance to these drugs, other drugs such as imipenem or fluoroquinolones (ciprofloxacin/moxifloxacin) can be considered based on antibiotic susceptibility, availability, and affordability. The mechanism of action, dose, route, side effects, and possible drug interactions of these drugs are shown in Table 17.4 [46, 47].

Table 17.4 Treatment options for endophthalmitis caused by gram-negative organisms[a] [46, 47]

Drug class	Beta-lactam	Aminoglycoside		Fluoroquinolone		Carbapenem
Drug name	Ceftazidime (Fortaz®)	Amikacin (Amikin®)	Gentamicin (Garamycin®)	Ciprofloxacin (Cipro®)	Moxifloxacin (Avelox®)	Imipenem (Primaxin®)
Mechanism of action	Interrupts cell wall synthesis via affinity for penicillin-binding proteins (PBPs). It is a third-generation cephalosporin	Interrupts bacterial protein synthesis by binding to the 30S ribosome of susceptible organisms	Interrupts bacterial protein synthesis by irreversibly binding the 30S subunit of the bacterial ribosome	Inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination	Inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination	Interrupts cell wall synthesis of various GPO and GNO and is a strong inhibitor of β-lactamases from some GNO that are resistant to most β-lactam antibiotics[b]
Route and dose	**Intravenous**—1 gm q8h or 2 gm q12h **Intravitreal—** 2.25 mg/0.1 ml **Topical**—50 mg/ml	**Intravenous**—7.5 mg/kg q12h **Intravitreal**—0.4 mg/0.1 ml **Topical**—20 mg/ml	**Intravenous**—2 mg/kg loading dose then 1.7 mg/kg q8h **Intravitreal**—0.2 mg/0.1 ml **Topical**—14 mg/ml	**Intravenous**—400 mg q12h or q8h **Intravitreal**—0.1 mg/0.1 ml **Topical**—0.3%	**Intravenous**—400 mg q24h **Intravitreal**—0.2 mg/0.1 ml (rabbits) **Topical**—0.3%	**Intravenous**—0.5 gm q6h, for *P. aeruginosa*—1 gm q6–8h **Intravitreal**—50 μg/0.1 ml **Topical**—na
Side effects with systemic dose	Eosinophilia, raised liver function tests, rash, positive Coombs, increased susceptibility to sunburn	Nephrotoxicity (renal tubular necrosis), deafness (cochlear toxicity),[c] vertigo (vestibular toxicity)	Nephrotoxicity (renal tubular necrosis), deafness due to cochlear toxicity, vertigo due to vestibular toxicity	Pseudomembranous colitis, CNS toxicity, skin rash, dysglycemia (hypo or hyper), photosensitivity, thrombocytopenia	Tendinopathy, chelation by multivalent cations, allergic reactions	Nausea, vomiting, diarrhea, raised liver function tests, seizures

(continued)

Table 17.4 (continued)

Drug class	Beta-lactam	Aminoglycoside		Fluoroquinolone		Carbapenem
Drug interactions	None	• Ototoxicity increases with cis-platinum, loop diuretics • Nephrotoxicity increases with amphotericin-B, loop diuretics, NSAIDS, cis-platinum, cyclosporine, radiographic contrast, vancomycin	• Ototoxicity increases with cis-platinum, loop diuretics • Nephrotoxicity increases with amphotericin-B, loop diuretics, NSAIDS, cis-platinum, cyclosporine, radiographic contrast, vancomycin	• Ciprofloxacin increases levels of caffeine, theophylline, cyclosporine, methadone • Cimetidine increases levels of ciprofloxacin	• Moxifloxacin increases Q-T interval in patients on antiarrhythmic drugs • Antacids, vitamins, didanosine, rifampin decrease absorption of moxifloxacin	• Imipenem decreases effectiveness of BCG, divalproex, valproic acid • Probenecid increases levels of imipenem

GPO gram-positive organisms, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *VRSA* vancomycin-resistant *Staphylococcus aureus*, *VISA* vancomycin intermediate-sensitive *Staphylococcus aureus*, *VRE* vancomycin-resistant enterococci, *CNS* coagulase negative staphylococci, *GNO* gram-negative organism, *na* information not available

Drugs by intravenous route are used for endogenous endophthalmitis cases

[a]The Sanford Guide To Antimicrobial Therapy 2016—46th Edition. Publisher—Antimicrobial Therapy, Inc.

[c]Amikacin—monthly audiogram, serum creatinine or BUN weekly if patient stable

[b]Imipenem is rapidly degraded by the renal enzyme dehydropeptidase when administered alone and is always coadministered with cilastatin to prevent this inactivation

Summary

Endophthalmitis caused by gram-negative bacteria presents with severe ocular inflammation and marked vision loss. Early treatment with intravitreal antibiotics and pars plana vitrectomy is necessary. Intravitreal steroids may help to decrease inflammation-induced damage to ocular tissue. Endophthalmitis caused by gram-negative bacteria are usually associated with poor prognosis despite prompt treatment.

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Frequently Asked Questions

1. *What are the clinical signs that differentiate from a gram-positive cocci endophthalmitis before culture results are available?*
   A: There are no known clinical signs that differentiate between endophthalmitis caused by gram-positive bacteria versus gram-negative bacteria.
   Suggested read—refer to section—Introduction for clinical presentation.

2. *Considering a restively poor outcome, should all gram-negative endophthalmitis receive a repeat intravitreal injection?*
   A: Repeat intravitreal injection should be considered on the basis of the initial response to intravitreal antibiotic and topical treatment. In cases with favorable response, topical treatment can be continued. However, in cases with worsening of features, repeat intravitreal injection or pars plana vitrectomy may be considered keeping in mind the antibiotic susceptibility results.

3. *Does intravitreal steroid play a crucial role in gram-negative endophthalmitis?*
   A: Ocular inflammatory response although important for the clearance of organisms during infection can induce damage to sensitive neurologic tissues. The ocular inflammatory response is induced by growing organisms and toxins produced (LPS, protein A) as well as by the metabolically inactive organisms. Antibiotic-induced release of cell walls or their components may therefore exacerbate intraocular inflammation during endophthalmitis treatment. Adjunctive use of corticosteroids has been shown to effectively suppress inflammation in cases of meningitis or otitis media [48, 49]. But for treatment of endophthalmitis, beneficial role of corticosteroid administration have been contradictory. Topical and subconjunctival corticosteroids are widely accepted. However, use of corticosteroids given via the systemic and intravitreal routes in the treatment of endophthalmitis remains controversial. In experimental models of bacterial endophthalmitis, concomitant

administration of dexamethasone was reported to be beneficial [50–53], had no effect [54], or was detrimental [55, 56] to infection outcome. Despite these conflicting results, intravitreal steroids are frequently used as an adjunct to antibiotic therapy in endophthalmitis [57].

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Chapter 18
Endophthalmitis Caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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Staphylococcus aureus is an important human bacterial pathogen responsible for a wide variety of ocular diseases, including sight-threatening infections such as keratitis, corneal flap melt after laser-assisted in situ keratomileusis (LASIK), cellulitis, endophthalmitis, and panophthalmitis [1–4]. *Staphylococcus aureus* isolates that are resistant to methicillin are known as methicillin-resistant *Staphylococcus aureus* (MRSA) and are usually also resistant to other β-lactam antimicrobial drugs [5]. In current practice, methicillin sensitivity is usually performed with oxacillin or cefoxitin, as methicillin is no longer commercially available in the United States. Oxacillin is more likely to maintain its activity during storage better than methicillin, while cefoxitin can give more reproducible and accurate results than tests with oxacillin or methicillin. The organisms are still called "MRSA" and not "oxacillin-resistant *Staphylococcus aureus*" or "cefoxitin-resistant *Staphylococcus aureus*" because of this historic role.

Organisms resistant to antibiotics pose great difficulty in the management of infection as compared to organisms that are susceptible to antibiotics in terms of treatment options, availability, affordability, and increased cost of alternative drugs. Endophthalmitis caused by drug-resistant organisms is an emerging concern, as well as a diagnostic and therapeutic challenge for treating physicians [5]. In cases of endophthalmitis, MRSA should be considered in patients with poor response to first-line treatment for presumed *Staphylococcus aureus* infections.

MRSA infection was first identified in the 1960s and occurs more frequently in patients with systemic diseases and previous infections with MRSA [6]. Reported risk factors for MRSA include increased age, previous or recent hospitalization, previous MRSA colonization, antibiotic use, and residence in an assisted living facility [7–9]. More frequent cases of endophthalmitis caused by MRSA are increasingly reported from around the world [10, 11]. The current chapter helps in

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understanding the importance of geographical distribution, various virulence factors, role of virulence factors in pathogenesis of endophthalmitis, mechanism of resistance, reported rates of resistance across the different geographical areas, and possible treatment options in the management of endophthalmitis caused by MRSA.

Prevalence

The prevalence of MRSA among ocular isolates varies around the world and has been reported ranging from 9.6% to 53% [12]. Of historic interest, in the Endophthalmitis Vitrectomy Study (EVS study, 1990–1994), MRSA was cultured in approximately 1.9% of isolates (6/323) from vitreous samples. The prevalence of MRSA as a cause of ocular infections including endophthalmitis is increasing over the past few decades. Ocular MRSA isolates have geographical differences with prevalence rates in the United States from 1.9% to 41% and in India at 34.1% [13, 14]. The European Cataract and Refractive Surgeons (ESCRS) study conducted throughout various countries in Europe did not report endophthalmitis caused by MRSA [15].

The prevalence rates of ocular infections caused by MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA) reported from various geographical areas are listed in Table 18.1 [1, 5, 6, 12–18]. Surveillance studies (including SENTRY Antimicrobial Surveillance Program; SMART, Study for Monitoring Antimicrobial Resistance Trends; or Ocular TRUST, Ocular Tracking Resistance in the United

Table 18.1 Prevalence of ocular infection with *Staphylococcus aureus* (including MSSA, MRSA, HA-MRSA, and CA-MRSA) reported in literature [1, 5, 6, 12–18]

Study (year)	Country	Infection	MSSA% (*N*)	MRSA% (*N*)	HA-MRSA	CA-MRSA
EVS group 1990 [17]	USA	Endophthalmitis	7.4 (24/323 isolates)	1.9 (6/323 isolates)	na	na
Freidlin et al. 2007 [16]	USA	Ocular	90.4 (827/915 isolates)	9.6 (88/915 isolates)	na	na
ESCRS group, 2008 [15]	Europe	Endophthalmitis	6.9 (2/29 patients)	0.0 (0/20 patients)	na	na
Asbell et al. 2008 [1]	USA	Ocular	83.2 (164/197 isolates)	16.8 (33/197 isolates)	na	na
Bagga et al. 2010 [14]	India	Ocular	65.9 (131/199 isolates)	34.1 (68/199 isolates)	na	na
Major et al. 2010 [13]	USA	Endophthalmitis	59.0 (19/32 patients)	41.0 (13/32 patients)	na	na

(continued)

Table 18.1 (continued)

Study (year)	Country	Infection	MSSA% (*N*)	MRSA% (*N*)	HA-MRSA	CA-MRSA
Hsiao et al. 2012 [5]	Taiwan	Ocular	47.2 (245/519 patients)	52.8 (274/519 patients)	93 patients	181 patients
Sun et al. 2012 [6]	Australia	Ocular	78.2 (391/500 isolates)	21.7 (109/500 isolates)	75 patients	5 patients
Vola et al. 2013 [12]	Brazil	Ocular	91.1 (510/566 isolates)	9.9 (56/566 isolates)	na	na
Hong et al. 2013 [18]	China	Ocular	43.2 (310/718 patients)	56.8% (408/718 patients)	146 patients	262 patients

CA-MRSA community-associated methicillin-resistant *Staphylococcus aureus*, *HA-MRSA* healthcare-associated methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *N* number, *na* information not available

Table 18.2 Rates of susceptibility to antimicrobials among methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA)

	BPEI data from the United States (Jan 2011–Dec 2015)		LVPEI data from India (Jan 2011–Dec 2015)	
	MSSA (%) (8/16 isolates)	MRSA (%) (8/16 isolates)	MSSA (%) (10/11 isolates)	MRSA (%) (1/11 isolates)
Oxacillin	100	0	100 (7/7)	ND
Cefoxitin	100	0	100 (10/10)	0 (0/1)
Fluoroquinolones[a]	63	0		
• Ciprofloxacin • Moxifloxacin • Ofloxacin			40 (4/10) 90 (9/10) 50 (5/10)	100 (1/1) 100 (1/1) 100 (1/1)
Linezolid	100	100	ND	ND
Daptomycin	100	100	ND	ND
Tigecycline	100	100	ND	ND
Vancomycin	100	100	90 (9/10)	100 (1/1)

MSSA methicillin-sensitive *Staphylococcus aureus, MRSA* methicillin-resistant *Staphylococcus aureus*, *ND* not done

[a]Fluoroquinolones include ciprofloxacin, moxifloxacin, and ofloxacin

States Today) carried out by the World Health Organization, United States Food and Drug Administration, and the Centers for Disease Control and Prevention (CDC), provide national and global information on infections caused by resistant pathogens [19–26]. The rates of susceptibility of ocular isolates of MRSA and MSSA to antimicrobials (Bascom Palmer Eye Institute from the United States and LV Prasad Eye Institute from India) over a 5-year period (January 2011–December 2015) are shown in Table 18.2.

Virulence Factors and Pathogenesis

Structural and secreted products of *Staphylococcus aureus* act as virulence factors. Virulence factors of *Staphylococcus aureus* are shown in Table 18.3. These surface proteins, secreted proteins, and cell wall components help in colonization, immune stimulation, and evasion. The pathogenesis is complex and involves multiple mechanisms. The virulence factors involved in the pathogenesis of *Staphylococcus aureus* infection are generally not unique for MRSA. So it is important to know the pathogenesis of both *Staphylococcus aureus* in general and MRSA.

Pathogenesis of Staphylococcus aureus—various factors/enzymes/toxins listed in Table 18.4 are responsible for pathogenesis of infection by *Staphylococcus aureus*. Adhesins from the MSCRAMMs ("microbial surface components recognizing adhesive matrix molecules") family mediate intracellular adhesion, aggregation, inflammation, and even immune evasion. Adhesins, enzymes, and toxins also contribute to internalization of bacteria into endothelial cells, invasion, and biofilm formation. Biofilm formation on the abiotic surfaces such as intraocular lenses and sutures may provide survival advantage to bacteria leading to persistent infection. Cytolysins produced by *Staphylococcus aureus* are involved in pathogenesis of endophthalmitis. In an experimental model, Booth et al. have reported that eyes infected with wild strain had more retinal damage and ocular inflammation as compared to *Agr* (accessory gene regulator) strain [27]. Experimental infection of vitreous with strains producing alpha and beta toxins seem to have more retinal dysfunction and inflammation compared to infection with mutant strains lacking these toxins [28]. These virulence factors lead to improved evasion of the host immune system or unique toxin production by these organisms.

Table 18.3 Virulence factors of *Staphylococcus aureus*

Surface proteins (expressed during replication phase)—help in colonization
• Protein A
• Coagulase A
• Elastin-binding protein
• Collagen-binding protein
• Fibronectin-binding protein
• Clumping factor
Secreted proteins (expressed in stationary phase)—help in spread of infection
• Enterotoxin-B
• TSST-1 (toxic shock syndrome toxin)
• α-toxin (hemolysin)
• Cytolysins
• Beta-toxin (sphingomyelinase)
Cell wall components
• Peptidoglycan
• Teichoic acid
• Capsule

Table 18.4 Pathogenesis of *Staphylococcus aureus*

1. Adhesion of bacteria to host tissue
(a) MSCRAMMs ("microbial surface components recognizing adhesive matrix molecules")—help in growth and persistence of bacteria by
• Biofilm formation (consisting of proteinaceous material, extracellular DMNA, and polysaccharides providing a foothold and physical barrier)
• Invasion and survival inside epithelial cells
• Small colony variant formation
2. Evasion of host immune system
(a) Production of antiphagocytic microcapsule
(b) Prevention of opsonization
(c) Interference with neutrophil extravasation/chemotaxis
(d) Leukocyte destruction by formation of pores in cell membranes
3. Enzymatic degradation
(a) Protease
(b) Lipase
(c) Elastase
4. Other toxins
(a) Exfoliative toxins
(b) Epidermolysis
(c) Super antigens
(d) Cytolysins
(e) α-toxin (hemolysin)
(f) Beta-toxin (sphingomyelinase)

Pathogenesis of MRSA—MRSA has certain factors and genes responsible for virulence and pathogenesis (Table 18.5) [29–38]. Gene "mec A" carried on a large mobile genetic element called staphylococcal cassette chromosome mec (SCCmec) confers methicillin resistance. SCCmecA gene encodes for an alternative penicillin-binding protein (PBP2a or PBP2b) with a lower affinity for β-lactams and allows survival to MRSA strain in different concentrations of these antimicrobial agents. Twelve major variants of SCCmec have been identified. Types I–II are more commonly associated with healthcare-associated MRSA (HA-MRSA) infections, while types IV–XII are associated with community-associated MRSA (CA-MRSA) infections. Panton-Valentine leukocidin (PVL) helps in tissue destruction and is more commonly associated with CA-MRSA infections. These factors conferring resistance to antibiotics lead to severe infection and inflammation in cases of endophthalmitis caused by MRSA.

Regulation of expression of virulence factors plays an important role in the pathogenesis of *Staphylococcus* infections. Virulence factor expression in *Staphylococcus aureus* is controlled by quorum sensing regulatory system such as *Agr*, *SarA*, *Sae*, and *Arl* [39]. *Agr* system regulates the production of secreted toxins and virulence factors. *SarA* system promotes synthesis of toxins (α, β, δ), fibronectin, and fibrinogen-binding adhesion involved in cytolysis and spread of infection. *SaeR/S* regulates survival of the organism during neutrophil phagocytosis. *Arl* system downregulates protein A.

Table 18.5 Pathogenesis of methicillin-resistant *Staphylococcus aureus* (MRSA)

1. Healthcare-associated MRSA (HA-MRSA)
(a) Genetic component—"SCCmec"
(b) SCCmec types I–III (more common)
2. Community-associated MRSA (CA-MRSA)
(a) Genetic component—"SCCmec"
(b) SCCmec types IV–XII
(c) Larger SCCmec types—associated with multidrug-resistant MRSA strains
3. PVL—Panton-Valentine leukocidin
(a) Cell lysis
(b) Release of enzymes and cytokines from neutrophil
(c) Apoptosis/necrosis of neutrophils
(d) Dermonecrosis

Biofilm formation—*Agr* and *SarA* systems regulate transition from planktonic to biofilm growth. Loss of *Agr* enhances the propensity to biofilm formation, while loss of *SarA* results in reduced biofilm formation [39].

MRSA Profiles

MRSA was traditionally associated with healthcare facilities, but its prevalence has increased in otherwise healthy patients without identified risk factors [5, 10]. MRSA profiles are distinguished into either healthcare-associated MRSA (HA-MRSA) or community-associated MRSA (CA-MRSA) [10, 40, 41]. These types are different from each other clinically, microbiologically, and genetically and are defined as follows:

Healthcare-associated MRSA (HA-MRSA) isolate is confirmed if the original entry criteria of hospitalization for more than 72 h before culture acquisition is met and if in the year before the present hospitalization, the patient had had any one of the following: hospitalization, surgery, residency in a long-term care facility, and hemodialysis or peritoneal dialysis or at the present admission had indwelling percutaneous devices or catheters [42]. These may have multidrug resistance, increased virulence, transmissibility, and the ability to colonize hosts [43]. Genotyping shows that these HA-MRSA are more often associated with SCCmec types I, II, and III.

Community-associated MRSA (CA-MRSA) is confirmed if the patient did not meet any of the above criteria and had an infection at the time of admission and the culture of the infection on admission was taken ≥72 h after admission. These are mainly involved in skin and soft tissue infections, often sensitive to other anti-staphylococcal agents, carry genes for Panton-Valentine leukocidin (PVL), and may present a new acquisition of type IV or type V staphylococcal cassette chromosome mec (SCCmec) DNA [43–45]. CA-MRSA is more commonly associated with SCCmec types IV to type XII on genotyping.

These MRSA profiles (HA-MRSA and CA-MRSA) are further classified phenotypically or genotypically. In phenotypic classification, demonstrating antibiotic resistance pattern, the HA-MRSA is more resistant to antibiotics (such as aminoglycosides, β-lactam, and fluoroquinolones) as compared to CA-MRSA. In genotypic classification, SCCmec types I–III are associated with HA-MRSA, and types IV–XII are associated with CA-MRSA. Currently, the number of CA-MRSA infections appears to be increasing, and the types responsible are noted in healthcare settings that make the distinction between the two types difficult [46, 47].

Ocular Infections by MRSA

MRSA can affect the eye in various forms such as blepharoconjunctivitis, keratitis, corneal flap melt after LASIK, cellulitis, dacryocystitis, endophthalmitis, panophthalmitis, etc. [16, 48–50]. A retrospective cross-sectional, 8-year study reported blepharoconjunctivitis as the most common diagnosis in both MRSA and MSSA groups. The reported incidence of MRSA among all ophthalmic infections has increased from 4.1% to 16.7% from 1990 to 2007 in the United States [16].

Endophthalmitis caused by MRSA—Staphylococcus aureus is an important and frequent cause of acute-onset endophthalmitis [51]. The patients may present with hypopyon, pain, and fibrinous exudates in the anterior chamber. The visual acuity at presentation is generally poor. Experimental (rabbit and rat) model of endophthalmitis has shown that α- and β-toxins contribute significantly to endophthalmitis. Mutation of both *SarA* and *Agr* loci lead to almost complete attenuation of intraocular virulence of *Staphylococcus aureus*.

Exogenous endophthalmitis—acute-onset postoperative endophthalmitis caused by MRSA is a severe and potentially blinding infection; the incidence is increasing [13, 52]. Endophthalmitis with MRSA is reported most commonly after cataract surgery and often has poor visual outcomes [53, 54]. In the EVS, MSSA was reported in 7.4% of isolates, and MRSA was reported in 1.9% of isolates [17]. The reported incidence of postoperative MRSA endophthalmitis between 1990 and 2007 increased from 1.9% to 18.2% in the United States [16]. This may be due to differences in the epidemiological features and geographical distribution [13].

The visual outcomes of endophthalmitis cases caused by MRSA have invariably poor. Deramo reported a retrospective, consecutive, observational series of MRSA-associated acute postoperative endophthalmitis occurring after cataract surgery over a period of 3 years [52]. In this case series, 18% (6/33) cases were culture positive for MRSA and were treated with topical fluoroquinolones during the preoperative period. Occurrence of endophthalmitis despite the use of topical fluoroquinolones is of concern as topical fluoroquinolones (preoperatively or postoperatively) are very commonly used as a measure of endophthalmitis prevention. All these organisms were susceptible to gentamicin and vancomycin but resistant to fluoroquinolone on in vitro antibiotic susceptibility tests. The visual outcomes were poor (hand motions or worse) in four of six eyes with no light perception in two eyes. Similarly, another

retrospective series of 32 patients with acute-onset endophthalmitis over a period of 13 years by Major et al. reported higher incidence of fluoroquinolone resistance among MRSA isolates (62%) compared to MSSA isolates (5%) [13]. MRSA was accounted for more than one-third of cases. Cataract surgery was the most common setting. The patients presented with hypopyon, pain, visible exudates in the anterior chamber, and poor presenting vision. All MRSA isolates were susceptible to vancomycin in this series. High rates of pars plana vitrectomy in the management of MRSA vs. MSSA were reported (61% vs. 47%) and possibly explain a more severe clinical presentation that required a vitrectomy. At 3 months follow-up, final visual acuity of 20/400 or better was reported in 36% of MRSA cases compared to 59% of MSSA cases.

Endogenous endophthalmitis—endogenous endophthalmitis caused by MRSA is rare [55]. Patients often have complex and interactive medical conditions such as immunocompromised status, immunosuppression, and chronic medical conditions including hypertension, diabetes mellitus, end-stage renal disease, intravenous drug abuse, lymphoma, and other serious health issues. Delay in the diagnosis, virulence of the causative organism, and the extent of intraocular inflammation are the predictors of final visual acuity [55, 56]. Visual outcomes in endogenous endophthalmitis caused by MRSA are usually poor. Most cases of endophthalmitis can be treated successfully with empirical antibiotics. However, it is important to identify the causative organism as well as the antibiotic susceptibilities in view of increasing antibiotic resistance so that appropriate and timely antibiotics could be used. Treatment includes pars plana vitrectomy, intravitreal, and systemic antibiotics.

Selected reports of MRSA endophthalmitis as reported in literature are shown in Table 18.6 [10, 13, 49, 52, 55–61].

Antibiotic Susceptibility Pattern

Antibiotic susceptibility patterns of MRSA to various antimicrobials reported in literature are shown in Table 18.7 [5, 6, 12–14, 16, 18]. Most of the studies report good susceptibility of MRSA to vancomycin. But MRSA is known for its tendency to acquire resistance easily. The strains are reported to have resistance to penicillin and variable resistance to fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin) [62, 63]. Recently cases of endophthalmitis caused by reduced vancomycin susceptibility and/or vancomycin resistance have been reported in literature [64]. Keeping in mind the principles of antibiotic stewardship, these results indicate the need for judicious use of antibiotics for prophylaxis and management [65]. In the meantime, continued vigilance, a strict enforcement of preventive measures, and the restricted use of glycopeptides both in human beings and animals represent our best response to the spread of multiresistant gram-positive cocci worldwide.

Table 18.6 Select cases of endophthalmitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) as reported in literature [10, 13, 49, 52, 55–61]

Report	Study duration	Place	Type	No of MRSA Cases	Antibiotic susceptibility of isolated MRSA	Outcome			Risk factors/comments
						Enucleation	<20/200	>20/200	
Exogenous endophthalmitis									
Deramo et al. 2008 [52]	3 years	USA	Exogenous	6/33	V (100%), G (100%)	None	4/6	2/6	Preoperative topical FQ
Major et al. 2010 [13]	17 years	USA	Exogenous	13/32	V (100%), G (54%), Clinda (61%), GFC (38%)	1/13	8/13	5/13	Increased age, recent hospitalization, antibiotic use
Endogenous endophthalmitis									
Romero et al. 1999 [57] (case report)	–	USA	Endogenous	1	na	1/1	None	None	DM and ESRD
Binder et al. 2003 [58] (case series)	18 years	USA	Endogenous	2/27	na	2/2	None	None	DM, ESRD, and IVDA
Schiedler et al. 2004 [59] (case series)	5 years	USA	Endogenous	2/21	na	None	1/2	1/2	Immunosuppressive therapy, DM, ESLD, and ESRD
Leibovitch et al. 2005 [60] (case series)	13 years	Australia	Endogenous	1/13	na	1/1	None	None	DM

(continued)

Table 18.6 (continued)

Report	Study duration	Place	Type	No of MRSA Cases	Antibiotic susceptibility of isolated MRSA	Outcome			Risk factors/comments
						Enucleation	<20/200	>20/200	
Rutar et al. 2006 [49] (case series)	6 months	USA	Endogenous	9	V (100%), Clinda (100%), R (100%), TMP-SMZ (100%)	1/9	1/9	8/9	IVDA, ESRD, DM, and AIDS
Blomquist et al. 2006 [10] (case series)	5 years	USA	Endogenous	1	na	1/1	None	None	IVDA
Burgess et al. 2007 [61] (case report)	–	USA	Endogenous	1	na	None	1/1	None	ESRD
Ness et al. 2009 [55] (case report)	–	Germany	Endogenous	3	na	1/3	3/3	None	Presence of systemic disease—2 patients (DM-1, lymphoma-1)
Ho et al. 2011 [56] (case series)	3 years	Michigan	Endogenous	7 (8 eyes)	V (100%), G (100%), TMP-SMZ (100%), T (100%), L (100%)	1/8	5/8	3/8	Presence of systemic disease—6 patients (DM-5, HTN-1)

AIDS acquired immunodeficiency syndrome, *Clinda* clindamycin, *DM* diabetes mellitus, *ESLD* end-stage liver disease, *ESRD* end-stage renal disease, *FQ* fluoroquinolone, *G* gentamicin, *GFC* gatifloxacin, *HTN* hypertension, *IVDA* intravenous drug abuse, *L* linezolid, *MRSA* methicillin-resistant *Staphylococcus aureus*, *na* information not available, *R* rifampin, *TMP-SMZ* trimethoprim-sulfasalazine, *T* tetracycline, *V* vancomycin

Table 18.7 Antibiotic susceptibilities of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from ocular infections as reported in literature [5, 6, 12–14, 16, 18]

Study (duration)	Type	Vancomycin (%)	Fluoroquinolones	Teicoplanin	Clindamycin	TMP-SMZ	Gentamicin	Tetracycline	Penicillin	Tobramycin
Freidlin et al. 2007 (8 years) [16]	MRSA	100 (na)	na	na	na	97.7%	na	93.2%	na	na
Bagga et al. 2010 (3 years) [14]	MRSA	100 (na)	MFC—40% GFC—67% OFC—25%	na	na	na	na	na	na	na
Major et al. 2010 (13 years) [13]	MRSA	100 (na)	MFC—38% CFC—54% (7)	na	61% (8)	92% (12)	54% (7)	na	0%	na
Hsiao et al. 2012 (10 years) [5]	CA-MRSA	100 (181)	na	100% (171)	10.5% (19)	85.1% (154)	na	na	0%	na
	HA-MRSA	100 (93)	na	100% (89)	5.4% (5)	64.5% (60)	na	na	0%	na
Sun et al. 2012 (10 years) [6]	CA-MRSA	100 (5)	CFC—60% (3)	na	80% (4)	80% (4)	80% (4)	na	na	na
	HA-MRSA	100 (75)	MFC—na	na	20% (15)	36% (27)	16% (12)	na	na	na
Vola et al. 2013 (10 years) [12]	MRSA	100 (na)	MFC—85% CFC—70% GFC—88%	na	na	na	70% (na)	na	na	56%

(continued)

Table 18.7 (continued)

Study (duration)	Type	Vancomycin (%)	Fluoroquinolones	Teicoplanin	Clindamycin	TMP-SMZ	Gentamicin	Tetracycline	Penicillin	Tobramycin
Hong et al. 2013 (6 years) [18]	CA-MRSA	na	CFC—72.9% OFC—61.1% GFC—87.0%	na	na	na	na	77.9%	na	na
	HA-MRSA	na	CFC—37.7% OFC—32.9% GFC—63.7%	na	na	na	na	52.1%	na	na

CFC ciprofloxacin, *Clinda* clindamycin, *CA* community-associated methicillin-resistant *Staphylococcus aureus*, *GFC* gatifloxacin, *HA-MRSA* healthcare-associated methicillin-resistant *Staphylococcus aureus*, *MFC* moxifloxacin, *MRSA* methicillin-resistant *Staphylococcus aureus*, *na* information not available, *OFC* ofloxacin, *TMP-SMZ* trimethoprim-sulfasalazine

Treatment Options

The treatment options for MRSA include vancomycin, daptomycin, linezolid, tigecycline, telavancin, and ceftaroline. In general, the drug of choice for MRSA endophthalmitis is vancomycin. The Infectious Diseases Society of America (ISDA) recommends the use of vancomycin alternatives for infections caused by isolates that have a minimum inhibitory concentration (MIC) >2 μg/ml [66]. As per the ISDA's most recent guidelines, alternatives are recommended for infections unresponsive to vancomycin. Cases of endophthalmitis caused by reduced vancomycin susceptibility and/or vancomycin resistance have been reported in literature [64]. A review published in 2014 reported poor visual outcomes (visual acuity worse than 20/400) in 16 of 26 endophthalmitis cases with reduced susceptibility to vancomycin [64]. Four endophthalmitis cases were reported to be *Staphylococcus aureus* infection. Increasing drug resistance poses a challenge for finding newer and effective drugs to control life- or organ- or sight-threatening infections. Drugs with fewest side effects and highest efficacies are needed. None of these drugs are currently FDA approved for the use in endophthalmitis.

The details of the individual drugs, routes, dosage, and potential adverse effects are mentioned in Table 18.8 [64, 67]. There is paucity of data in the literature about the outcomes of these drugs for endophthalmitis cases. So the treatment of cases of endophthalmitis has to be individualized keeping in mind the availability, cost, antibiotic susceptibility of the causative organism, potential adverse effects, and severity of the infection.

Prevention Strategy

Staphylococcus aureus primarily colonizes the anterior nares. Other sites of colonization include the nasopharynx, skin (especially skin folds), perineum, axillae, and the gastrointestinal tract. Patients who are carriers of *Staphylococcus aureus* (MRSA and MSSA) are at higher risk of developing surgical site infections [68].

Certain screening and treatment measures are advised for decontamination/decolonization of hospitalized patients. Strategies to reduce prevalence of MRSA include:

- Isolation practices (contact precautions/the use of gloves)
- Hygiene measures (handwashing)
- Screening and decolonization policies
- Overall antibiotic controls

Joshi et al. reported active screening of MRSA being performed for patients who are transferred from any inpatient healthcare facility, entering or leaving any intensive care unit, or undergoing preadmission testing for any inpatient surgical procedure [69]. Decolonization is the process of eradicating or reducing asymptomatic

Table 18.8 Treatment options for endophthalmitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA)[a] [64, 67]

	Vancomycin (Vancocin®)	Linezolid (Zyvox®)	Ceftaroline fosamil (Teflaro®)	Quinupristin/ dalfopristin (Synercid®)	Daptomycin (Cubicin®)	Telavancin (Vibativ®)
Class	Glycopeptide	Oxazolidinone (fermentation by-product of *Streptomyces roseosporus*)	β-lactam antibiotic (fifth-generation cephalosporin)	Streptogramin (isolated from *Streptomyces pristina spiralis*)	Cyclic lipoglycopeptide	Glycopeptide
Mechanism of action	Inhibits synthesis and cross-linking of the NAM/ NAG polymers that form the backbone of the bacterial cell wall	Inhibits initiation of protein synthesis by binding 23S rRNA of the 50S subunit of bacterial ribosome	Binding to the penicillin-binding protein 2a (PBP2a)	Inhibits bacterial protein synthesis by interfering with function of 23S RNA (quinupristin-dalfopristin = 3:7)	Terminates bacterial DNA, RNA, and protein synthesis and cell death by forming transmembrane channels in cell membrane and depolarization of membrane potential	Inhibits bacterial cell wall synthesis by binding to the D-Ala-D-Ala terminus of the peptidoglycan in the growing cell wall. In addition, it disrupts bacterial membranes by depolarization
Route and Dose	Intravenous—7.5 mg/kg q8h Intravitreal—1 mg/0.1 ml Topical—50 mg/ml Oral—125 mg 4 times a day	Intravenous—600 mg q12h Intravitreal—300 μg/0.1 ml (rabbits) Topical—2 mg/ml (rabbits) Oral—600 mg twice daily	Intravenous—600 mg q12h (non-ocular infections)[b] Intravitreal—not available Topical—not available Oral—not available	Intravenous—7.5 mg/kg q8h Intravitreal—0.4 mg/0.1 ml In vitro—MIC_{90}—0.5–2 (mg/l)	Intravenous—4–6 mg/kg per day Intravitreal—200 μg/0.05 ml (rabbits) Topical—1% (rabbits)	Intravenous—10 mg/kg q24h Intravitreal—not available Topical—not available

	Vancomycin (Vancocin®)	Linezolid (Zyvox®)	Ceftaroline fosamil (Teflaro®)	Quinupristin/ dalfopristin (Synercid®)	Daptomycin (Cubicin®)	Telavancin (Vibativ®)
Side effects with systemic dose	Nephrotoxicity, red neck syndrome, rash, immune thrombocytopenia, fever, neutropenia	Reversible myelosuppression, irreversible peripheral neuropathy, optic neuropathy (when used for >14 days)	Nausea, headache, diarrhea, pruritus, and rash	Arthralgia, myalgia, pain, and periphlebitis at injection site	Not significant Minor gastrointestinal disturbances, pulmonary hypersensitivity reaction, and myopathy (Nanninin et al)	Avoid in pregnancy (teratogenic in animals), dysgeusia, nausea, vomiting, evidence of renal injury
Spectrum of activity	GPO (*Streptococcus*, *Staphylococcus*, and *Bacillus* species)	GPO, MRSA, VRSA, VISA, VRE, CNS, GNO, mycobacteria	MRSA, VRSA, VISA, aerobic and anaerobic GPO, aerobic GNO	MRSA, VISA, VRSA, *Streptococcus* species, CNS	MRSA, VRSA, VRE, *Staphylococcus, Streptococcus, Enterococcus*	MSSA, MRSA, other GPO
Others	Initial doses based on actual weight, including for obese patients If ineffective, consider other alternative drugs (ceftaroline, daptomycin, linezolid)	First pharmacologically active oxazolidinone (fermentation by-product of *Streptomyces roseosporus*) Good intraocular availability after intravenous and oral administration	No published data available at present on ocular safety and intraocular penetration	First intravitreal (0.4 mg/0.1 ml) use of quinupristin/ dalfopristin acute postoperative endophthalmitis in 2011	Pharmacokinetics are linear at dose of 4–12 mg/kg/day Available only in intravenous formulation	If weight of patient is 30% or more over ideal body weight, then dose calculated using adjusted body weight

GPO gram-positive organisms, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *na* information not available, *VRSA* vancomycin-resistant *Staphylococcus aureus*, *VISA* vancomycin intermediate-sensitive *Staphylococcus aureus*, *VRE* vancomycin-resistant enterococci, *CNS* coagulase-negative staphylococci, *GNO* gram-negative organism

[a]The Sanford Guide To Antimicrobial Therapy 2016—46th Edition. Publisher—Antimicrobial Therapy, Inc.

[b]Dose for complicated skin and soft tissue infections and community-acquired pneumonia

carriage of MRSA by giving appropriate antibiotics as recommended by the hospital policy. Decolonization may include the use of body wash (triclosan 1% or chlorhexidine gluconate 4%—bathe or shower for 2 days prior to surgery), nasal ointment (mupirocin 2% ointment), throat gargles (0.2% chlorhexidine-based mouthwash), etc. [68, 70]. A recent systematic review suggested some, but not robust, evidence in favor of universal decolonization to prevent surgical site infection [70]. Real-time PCR and other newer diagnostic techniques may be utilized in quick detection of the nasal carriage status in under 2 h and have made it possible to identify carriers shortly before surgery.

The rapid screening provides an opportunity for prophylactic decolonization and prevention of infection. It is important to note that decolonization offers temporary reduction of organisms from the site of carriage. Although literature in the ophthalmic surgery is scanty, these guidelines may be helpful in the areas endemic with MRSA infection. The infection control department should monitor risk factors for MRSA colonization and hospital staff compliance with MRSA screening procedures. The guidelines set forth by the CDC, and the Association for Professionals in Infection Control and Epidemiology should be followed to prevent the infection with MRSA. Long-term strategies are adopted so that the active MRSA surveillance and rapid MRSA disease diagnosis is possible in endemic situations.

Important Clinical Trials Involving Antibiotic Sensitivities

1. *The Ocular Tracking Resistance in the United States Today (Ocular TRUST) study.*
   The ocular TRUST (2005–2006) is the first nationwide longitudinal surveillance program to monitor antimicrobial susceptibility of ocular isolates. An independent central laboratory tested the antimicrobial susceptibility (in vitro) of ocular isolates collected prospectively from 34 institutions annually. The study reported MRSA in 16.8% ocular isolates, and these were highly resistant to fluoroquinolones (≥75%), azithromycin (90.9%), and tobramycin (63.6%). The ocular TRUST concluded with the need to consider alternative therapy to fluoroquinolone when MRSA was suspected. The ocular TRUST study and the Surveillance Network showed higher resistance to antimicrobials for MRSA compared to MSSA.
2. *The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study.*
   The ARMOR study of isolates from patients with bacterial eye infections conducted by 34 institutions across the United States in 2009 reported that MRSA isolates constituted 39% (78/200) of *Staphylococcus aureus* isolates. These 78 MRSA isolates in this study were more likely to be resistant to other drug classes as compared to 122 MSSA isolates (macrolides, fluoroquinolones, lincosamide, and aminoglycosides; $p < 0.0001$) as determined by microbroth dilution. MIC_{50}

(minimum inhibitory concentration inhibiting the growth of 50% of all isolates) and MIC_{90} (minimum inhibitory concentration inhibiting the growth of 90% of all isolates) of MRSA were reported higher compared to MSSA isolates from bacterial eye infections.

Conclusion

Endophthalmitis caused by MRSA is a serious problem with reported poor outcomes. These drug-resistant organisms have increased virulence and need prompt and aggressive treatment. Early detection of the causative organism along with the treatment guided by culture sensitivity test results are crucial in the management of endophthalmitis cases caused by MRSA to achieve the best possible outcomes.

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Frequently Asked Questions

1. *How different is methicillin-resistant Staphylococcus aureus infection from methicillin-sensitive Staphylococcus aureus infection?*
   A: The patients may present with significant hypopyon, pain, and fibrinous exudates in anterior chamber. The visual acuity at presentation is also poor. There are no comparative clinical trials of MRSA vs. other organism infection.
2. *What precautions are required to reduce the incidence of MRSA proliferation?*
   A: Suggested read—refer to section "Prevention Strategy."
3. *What is the suggested management for case of endophthalmitis with suspected MRSA?*
   A: Proceed with initial tap and inject with vancomycin and ceftazidime. If not responding, then consider early pars plana vitrectomy in these cases. The use of other drugs such as linezolid, quinupristin/dalfopristin, or daptomycin is based on cost/availability/affordability.
4. *What is the suggested management for case of endophthalmitis with confirmed MRSA?*
   A: Proceed with initial tap and inject with vancomycin and ceftazidime. If clinical response is favorable, continue topical antibiotics, and consider repeat intravitreal vancomycin.

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Chapter 19
Nocardia Endophthalmitis

Lalitha Prajna

Nocardia is an aerobic actinomycetes found in soil, wet mud, decomposing plant material, dust, and air [1]. *Nocardia* is Gram-positive, bacillary, branching bacteria whose hyphae often fragment to coccobacillary forms. Though distributed worldwide *Nocardia* species is more endemic in some areas especially dry and humid regions [1–4]. It rarely causes infection in immunocompetent persons. Patients who get systemic infection with *Nocardia* like pulmonary or disseminated infection are mostly immunosuppressed [5]. Endogenous *Nocardia* endophthalmitis also occurs in immunosuppressed people; exogenous endophthalmitis occurs mostly due to trauma and external entry of the organisms [6–11].

There is some confusion surrounding the taxonomic history of the genus *Nocardia*. This genus was first described by Edmond Nocard, a French veterinarian, who isolated a filamentous aerobic organism from cattle with farcy in 1888 [12]. *Nocardia asteroides* is now accepted as the type species of the genus *Nocardia*, and recently several studies have contributed to the formation of a homogeneous group of *Nocardia*. The genus *Nocardia* has been recently reviewed based on current molecular taxonomy. There are currently more than 30 species of *Nocardia* of human clinical significance, and the majority of isolates are *N. nova complex*, *N. abscessus*, *N. transvalensis complex*, *N. farcinica*, *N. asteroides type VI* (*N. cyriacigeorgica)*, and *N. brasiliensis* [1–3]. These species cause a wide variety of diseases and have variable drug susceptibilities. Recent application of modern taxonomic procedures and molecular characterization has expanded our knowledge of the phylogenetic relatedness and taxonomic status of this genus *Nocardia* [1, 2].

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Pathogenesis and Risk Factors

The majority of systemic nocardial infections are acquired through inhalation. The dry, dusty, and often windy conditions in the regions that have a high incidence of *Nocardia* in the soil may facilitate the aerosolization and enhance their acquisition via the respiratory route. A smaller number of infections are caused by traumatic percutaneous introduction of organisms [1, 2]. This maybe the case in exogenously acquired *Nocardia* endophthalmitis. We do not know much about the pathogenesis of ocular *Nocardia* infections because the occurrence of *Nocardia* infection, either systemic or ocular, is limited to only case reports or small case series.

Clinical Features

Postoperative and Traumatic Endophthalmitis

Exogenous *Nocardia* endophthalmitis is rare. The literature shows only few reports that describe exogenous endophthalmitis, after any ocular surgery or after trauma. The early reports were by Meyer et al. and Chen [13, 14]. The clinical presentation of *Nocardia* endophthalmitis is the characteristic yellowish white nodules in the anterior chamber and iris nodules (Fig. 19.1).

One of the largest series of post-cataract *Nocardia* endophthalmitis described in the literature is a study of 24 cases that occurred over a 4-year period. This included 196 cases of postoperative endophthalmitis from 304,944 cataract surgeries. *Nocardia* endophthalmitis was suspected in cases based on the characteristic clinical features of yellow-white nodules in the anterior chamber (distinctive from bacterial and fungal). These cases presented early with a mean duration of 6 weeks [9]. In other reports of postoperative *Nocardia* endophthalmitis, the clinical presentation was also similar with fluffy white cotton ball-like exudates in the anterior chamber and exudates surrounding the intraocular lens and capsular bag [11, 15]. The presentation of *Nocardia* endophthalmitis after cataract surgery is generally thought to be late presenting even after a few months [16]. However, in other reports the presentation was much earlier, presenting even within 6 weeks of surgery [9, 17]. So *Nocardia* must be suspected in patients from endemic regions who present with an abscess or nodule at the incision site even if it presents early on in the course of the disease. The various clinical pictures of post-cataract surgery *Nocardia* endophthalmitis are shown in Fig. 19.1.

Cases with traumatic endophthalmitis may have more varied presentation depending on the severity of the trauma. But the characteristic feature of “fluffy white or yellow nodules” in the anterior chamber or on the iris will still be present [10]. Sometimes it could be overwhelming (Fig. 19.2).

Other reports of exogenous *Nocardia* endophthalmitis caused by new species are reported recently. In an immunocompetent child, endophthalmitis was caused by

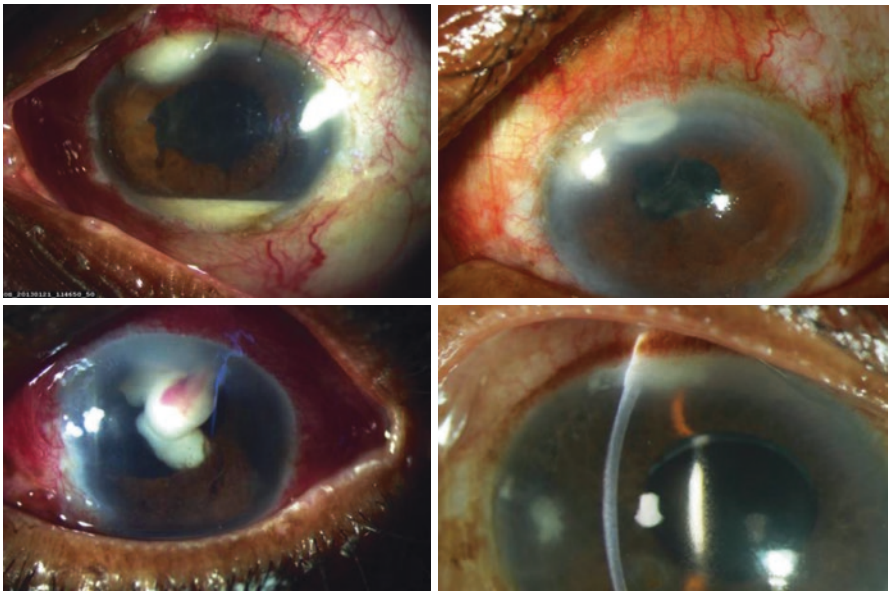

Fig. 19.1 Post-cataract surgery *Nocardia* endophthalmitis. (*Top left*) Yellow-white nodule at surgical section and hypopyon; (*top right*) anterior chamber nodule with fibrin formation; (*bottom left*) yellow-white nodules at the tunnel site; (*bottom right*) nodules in the paracentesis site and tunnel site superiorly

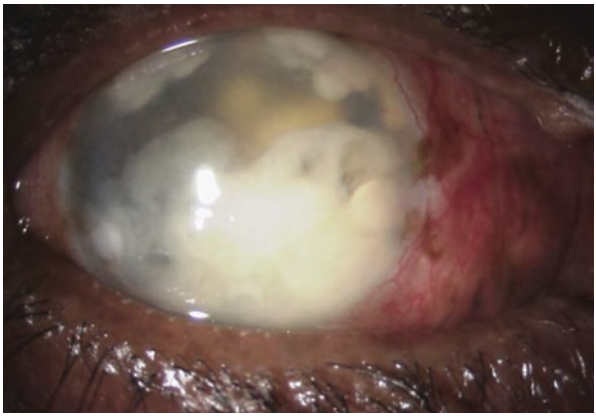

Fig. 19.2 Traumatic endophthalmitis—the entire anterior chamber is filled with yellow-white nodules

Nocardia kruczakiae after vegetable trauma presenting as late as 2 months [18]. Similarly, *Nocardia farcinica* causing infection of a Baerveldt implant and endophthalmitis in a patient with a Boston type I keratoprosthesis and *Nocardia brasiliensis* endophthalmitis in a patient with an exposed Ahmed glaucoma drainage implant are reported [19, 20]. In these cases the infection resolved with aggressive surgical and medical treatment.

Endogenous Endophthalmitis

Endogenous endophthalmitis occurrence is rare. It invariably occurs in immunocompromised patients. Nocardiosis is a serious life-threatening complication in immunosuppressed patients. In recent years isolated cases of *Nocardia* endogenous endophthalmitis have been reported. The clinical scenarios are varied from chronic steroid use and renal transplant [6, 7, 21–23]. It has also been reported as a rare sequel of pulmonary nocardiosis and from disseminated nocardiosis [24, 25]. *Nocardia* infection should be considered in any patient with atypical lung nodules and panuveitis. So patients who are systemically immunosuppressed are at greatest risk, and early suspicion of the role of this organism is paramount.

The first presenting sign of any systemic *Nocardia* infection may be ocular symptoms as is seen in many reports. In endogenous endophthalmitis signs are often limited to the posterior segment like panuveitis and yellowish, elevated subretinal lesion [21, 26]. Vitreous opacities and retinal detachments have also been described [6, 24]. Severe anterior chamber inflammation with fibrin formation is seen when the infection spreads to the anterior chamber.

Laboratory Diagnosis

Appropriate specimen selection is very important for proper isolation of *Nocardia*. The specimen must be representative of the disease. Haripriya et al. reported higher culture positivity with the anterior chamber aspirate in their series of post-cataract *Nocardia* endophthalmitis [9]. At the same time, the corneal and scleral specimens showed 100% positivity on the first sampling when the infection was confined to the surgical wound or in cases of scleral abscess [9]. Vitrectomy and a subretinal biopsy may be required for deep-seated infections. Conventional microscopy, culture, histopathology, and molecular diagnosis aid in confirming the etiological diagnosis [26]. However, it is not unusual for all specimens to be conventional culture negative and negative even by molecular tests since the 16S rRNA primer used for the universal identification of bacteria may not be sufficient to pick up *Nocardia* from ocular samples [27].

Specimens are inoculated directly onto 5% sheep blood agar, chocolate agar, brain heart infusion broth, and thioglycolate broth and incubated at 37 °C for 1 week. A Sabouraud dextrose agar is also inoculated and incubated at 25 °C for 2 weeks for fungal isolation. A direct microscopy for Gram stain, 10% potassium hydroxide, and a partial acid-fast stain must be done on the direct specimens.

On Gram stain, *Nocardia* is Gram-positive, bacillary, branching bacteria whose hyphae often fragment to coccobacillary forms (Fig. 19.3, top left). In 10% KOH wet mount, the filaments can be characteristically seen as thin filaments (Fig. 19.3, top right). A definite diagnosis is the detection of the organism directly from the specimen and growth on culture. As *Nocardia* is slow growing, plates have to be kept for extended period of time and regularly examined whenever *Nocardia* is

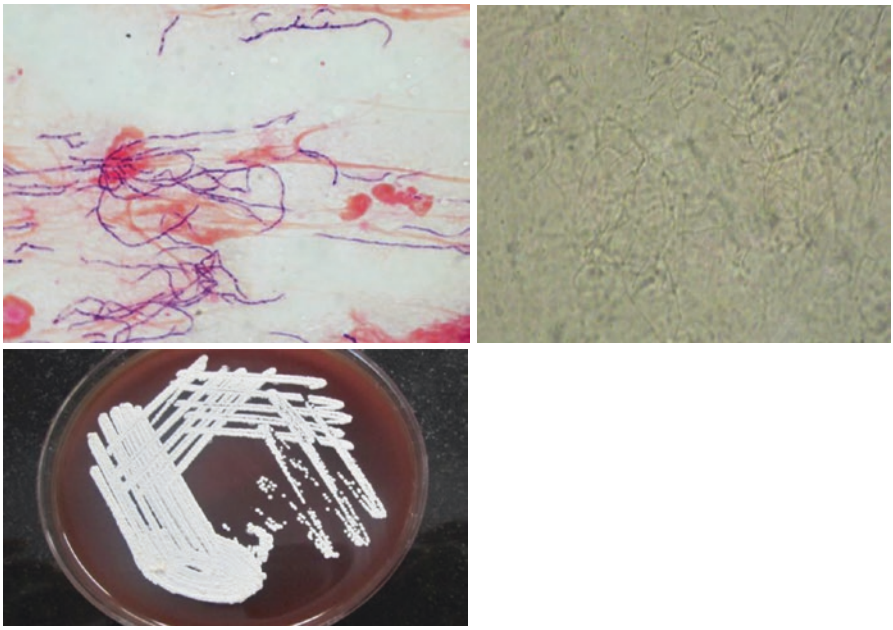

Fig. 19.3 Laboratory diagnosis of *Nocardia*. (*Top left*) Gram-positive beaded filaments on Gram stain from a sample of aqueous humor; (*top right*) 10% potassium hydroxide wet mount showing *Nocardia* filaments; (*bottom left*) blood agar plate showing the characteristic chalky white colonies of *Nocardia*

suspected. Colony morphology may vary depending on the species, but most are described as chalky with colonies which may later produce colored pigments (Fig. 19.3, bottom left). Species-level identification is difficult for most of the microbiology laboratories, and this can be done in reference laboratories [1, 2].

All clinical significant isolates of *Nocardia* must be tested for antibiotic sensitivities. The common antibiotics tested against are amikacin, gentamicin, vancomycin, cefazolin, ceftazidime, ciprofloxacin, ofloxacin, and sulfonamides or trimethoprim-sulfamethoxazole. Antibiotic sensitivities can be done by the Kirby-Bauer disk diffusion method or by micro-broth dilution method. This is sometimes difficult for laboratories that do not do this regularly and may have to send it to a reference laboratory. The Clinical Laboratory Standards Institute (CLSI) has published an approved standard for susceptibility testing for both mycobacteria and aerobic actinomycetes [2, 28].

Treatment

Aggressive management is needed for control of the infections. Although *Nocardia* is a low virulent organism, it has a tendency to persist, and it is very difficult to eradicate. Vitrectomy, sector iridectomy of the iris mass with repeat injections of

intravitreal antibiotics may be needed in the majority of cases. Intraocular lens extraction along with the bag may be the only way to limit the spread of infections in pseudophakic endophthalmitis.

Majority of endogenous *Nocardia* endophthalmitis has poor outcomes and often results in enucleation; there are also reports of death in extreme cases [22, 29]. There are exceptions, of course, when endogenous *Nocardia* endophthalmitis did not result in enucleation [6]. In many of these cases, delay in treatment due to initial misdiagnosis contributed to the morbidity and mortality. It is important that *Nocardia* be considered in the differential diagnosis in any immunosuppressed patient, including those receiving steroids, who presents with signs of intraocular infection.

Intravitreal injections: Amikacin (400 μg in 0.1 ml) is the drug of choice for intravitreal injections in proven cases of *Nocardia* endophthalmitis. It could be repeated after 24 or 48 h depending on the clinical response. One should be aware of macular infarction related to intravitreal amikacin [15].

Vitrectomy in *Nocardia* endophthalmitis should be as complete as possible.

Topical eye drops: Amikacin is the drug of choice. Fortified topical 2% amikacin hourly should be considered in the presence of any active corneal infiltrate.

Systemic antibiotic: Combined trimethoprim-sulfamethoxazole (TMP-SMX; co-trimoxazole) is the drug of choice in pulmonary or disseminated nocardiosis. Other drugs for parenteral use with activity against *Nocardia* include amikacin, imipenem, meropenem, ceftriaxone, and cefotaxime; each of these drugs can be used as part of combination therapy in severely ill patients. Active oral agents include sulfonamides, minocycline, and amoxicillin. Treatment is often very prolonged for up to 3 months [4, 5].

Frequently Asked Questions

1. *What clinical features differentiate Nocardia endophthalmitis from fungal infections?*
   A: The most **c**haracteristic clinical feature differentiating *Nocardia* endophthalmitis from fungal endophthalmitis is the presence of yellow-white nodules in the iris and anterior chamber. If it is an exogenous endophthalmitis, these nodules may be present in the wound site or as an infiltrate at the corneal tunnel or at the paracentesis site. Hypopyon is present in the majority of cases. B-scan may show vitreous opacities and retinochoroidal thickening. Fungal endophthalmitis may present as soft white cotton balls.

2. *When do we suspect post-cataract Nocardia endophthalmitis?*
   A: *Nocardia* endophthalmitis is suspected if the patient is from a known endemic area of *Nocardia* such as the dry windy and humid areas of South India and some regions of the USA and Africa. It should be suspected even if the case presents in the early postoperative period with an infiltrate at the section and yellow-white

cotton ball nodules in the anterior chamber or iris. The laboratory must be intimated about the suspicion of *Nocardia* and have them specially look this organism as this may be slow growing and could be mistaken for other Gram-positive bacilli.

3. *When is endogenous Nocardia endophthalmitis suspected?*
   A: This should be suspected in any immunocompromised patients with any underlying lung disease. Endophthalmitis could be the first presenting sign before any systemic infection is picked up.

4. *What specific request is made to the microbiology service when Nocardia endophthalmitis is suspected?*
   A: It is good to alert the laboratory before sending the samples when *Nocardia* endophthalmitis is suspected. This allows the laboratory to use special staining procedure (such as 1% acid-fast stain) and hold the media for longer periods. A repeat sample, when possible, improves the chance of recovery.

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Chapter 20
Bacillus Endophthalmitis

Vivek P. Dave and Joveeta Joseph

The genus *Bacillus* consists of aerobic bacilli known to form heat-resistant spores. They are Gram-positive organisms with their spores ubiquitously present in soil, air, and water. In the eye, *Bacillus* species are known to cause conjunctivitis, dacryocystitis, and also vision-threatening infections like endophthalmitis [1–7]. *Bacillus* spp. were first described in 1891 as a cause of endophthalmitis. Over the years, it has been recognized as the commonest microbiologic etiology in endophthalmitis following penetrating trauma [8–11]. *Bacillus* is also known to cause endogenous endophthalmitis [12–14] and postoperative endophthalmitis [15, 16]. The presenting symptoms include variable pain, redness, inflammation, and decreased visual acuity. The clinical signs include eyelid edema, conjunctival chemosis, corneal edema, hypopyon, fibrinous membrane in the anterior chamber or on intraocular lens (ILO), vitritis, and periphlebitis. Extensive spread of infection can lead to a corneal abscess and panophthalmitis.

Microbiology

Ubiquitous in nature, this genus is one of the largest group embracing more than 25 genera and over 200 species and includes both free-living and *pathogenic* species. *Bacillus* species are Gram-positive rods, aerobic, or facultatively anaerobic bacteria often arranged in pairs or chains with rounded or square ends (Fig. 20.1), and under stressful environmental conditions, the bacteria can produce oval *endospores* [17]. In recent years, there has been a taxonomic development in two selected groups of the genus *Bacillus*. They are called the *B. subtilis* group and the *B. cereus* group [18].

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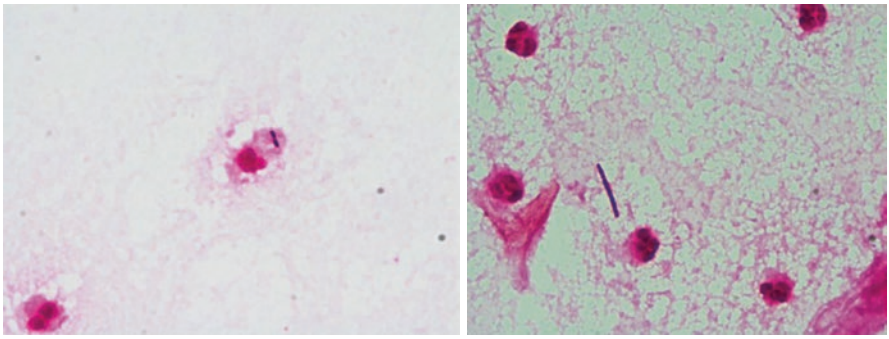

Fig. 20.1 Gram stain of vitreous aspirate showing multiple neutrophils along with Gram-positive thick bacilli (intracellular [*left*] and extracellular [*right*]) in oil immersion field (×1000)—bamboo stick appearance

The *Bacillus cereus* group includes *B. anthracis*, *B. cereus*, *B. mycoides*, *B. pseudomycoides*, *B. thuringiensis*, and *B. weihenstephanensis*. Most species are hemolytic, aerobic, or facultatively anaerobic, and most species are motile (a notable exception is *Bacillus anthracis*) by peritrichous flagella. Cells of these organisms are wider than 1 μm, sporangia are not swollen, and spores are ellipsoidal. They are, in principle, mesophilic and neutrophilic, and classical features to distinguish this group from all other aerobic endospore-forming bacteria are by their inability to produce acid from mannitol and their production of lecithinase [18]. Most species are oxidase positive, which may lead to confusion with *Pseudomonas* species, especially if the *Bacillus* species are poorly stained.

The *Bacillus subtilis* group is closely related and not easily distinguishable. They include *B. subtilis* subsp. *subtilis*, *B. subtilis* subsp. *spizizenii*, *B. mojavensis*, *B. vallismortis*, *B. clausii*, *B. atrophaeus*, *B. amyloliquefaciens*, *B. licheniformis*, *B. sonorensis*, *B. firmus*, *B. lentus*, and *B. sporothermodurans*. Cells of these organisms are less than 1 μm wide, sporangia are not swollen, and spores are ellipsoidal. They are in general mesophilic with regard to temperature, are neutrophilic with respect to pH for growth, and are often tolerant to higher pH levels [18].

Incidence and Species

The number of large studies describing the prevalence of *Bacillus* endophthalmitis is sparse. A decade ago, the incidence of *Bacillus* endophthalmitis was reported to be 4% in postoperative infection and 14.4% following trauma [19, 20]. The largest series till date, reported in 2001, included 31 cases of *Bacillus* endophthalmitis [21]. In this series, 90.3% cases were secondary to trauma. The commonest species across studies causing endophthalmitis has been *Bacillus cereus*. Other known species to cause endophthalmitis are *Bacillus subtilis*, *Bacillus licheniformis*, *Bacillus laterosporus*, and *Bacillus macerans*.

Pathogenesis and Virulence Mechanisms

Bacillus species are known to produce several toxins during intraocular growth. These include phospholipases, enterotoxins, hemolysins, and proteases [22, 23]. These toxins set up an intense intraocular inflammation that causes extensive tissue necrosis. In addition to the toxins, *Bacillus* shows a unique behavior among all Gram-positive organisms. Once inoculated into the eye, the *Bacillus* rapidly migrates to all parts of the eye from the anterior chamber to the retina within 6 h [24]. This leads to a prolific spread of infection and clinical worsening in the first 6–12 h if not treated timely, often resulting in the loss of the eye.

Antimicrobial Susceptibilities

As *Bacillus* is a Gram-positive organism, the first proposed combination for intraocular usage was clindamycin with gentamicin [25]. Vancomycin is as potent as clindamycin against *Bacillus.* Currently the commonly used drug for empiric management is intravitreal vancomycin. *Bacillus* is known to produce a β-lactamase enzyme, which makes it inherently resistant to penicillin group of antibiotics. In previously reported literature, the susceptibility of the *Bacillus* isolates to amikacin, gentamicin, and ciprofloxacin was over 90% [21]. We analyzed data of 86 eyes with *Bacillus* endophthalmitis [26]. In our study there was over 95% sensitivity to vancomycin, ciprofloxacin, and amikacin. Thus vancomycin continues to be the preferred intravitreal antibiotic for *Bacillus* endophthalmitis. Oral ciprofloxacin is the preferred antibiotic for systemic usage; the adult dose is 750 mg two times a day. This calculation is based on the fact that vitreous concentration of one 750 mg dose of ciprofloxacin exceeds the minimum inhibitory concentration for *Bacillus* [21]. The antibiotic sensitivity of two large series from the LV Prasad Eye Institute is shown in the Table 20.1.

Table 20.1 Antibiotic susceptibility profile of *Bacillus* species of a recent unpublished series ($n = 86$) in comparison to earlier series ($n = 31$) from the same clinical setup

Antibiotic	Percentage sensitivity in 2001 (Das et al. [21])	No. of isolates sensitive ($n = 31$, reported in 2001)	Percentage sensitivity in 2016 (Dave et al. [26])	No. of isolates sensitive ($n = 86$)
Amikacin	87.09	27	98.83	85
Cefazolin	64.51	20	47.67	41
Ciprofloxacin	83.87	26	98.83	85
Chloramphenicol	90.32	28	95.34	82
Gentamicin	93.54	29	100	86
Vancomycin	67.74	21	94.18	81

Role of Early Vitrectomy

Though the role of early vitrectomy has not been studied in humans, studies in a rabbit model have suggested a definite role of early vitrectomy [27]. In this model, it was shown that vitrectomy was effective in preserving significant retinal function if the surgery was initiated in the first 4 h following endophthalmitis. Though the results may not be extrapolated accurately to humans, it underlines the importance of prompt surgical management in cases of *Bacillus* endophthalmitis.

Diagnosis

Accurate and immediate identification of the infecting organism causing endophthalmitis is important for appropriate management. Standard microbiologic diagnostic methods include smear preparation for Gram stain and growth on selected culture media. Most *Bacillus* spp. grow readily on nutrient agar or peptone media. Growth is sometimes improved by glucose, but not by blood or serum. The optimum temperature for growth varies from 25 to 37 °C. The commonly used media are chocolate agar, 5% sheep blood agar, brain heart infusion broth, and thioglycollate broth. In the vegetative form, the bacilli are killed in 1 h by moist heat at a temperature of 55 °C. The spores of *B. subtilis* may withstand boiling for hours.

Identification is confirmed by Gram stain as described above (large Gram-positive to Gram variable rods, arranged in pairs or chains with rounded or square ends). In the *B. cereus* group, colonies grown on culture media appear flat and irregular and are 2–5 mm in diameter with a gray/white color and ground-glass appearance on blood agar with β hemolysis. Colonies show a tenacity that allows them to be pulled up and stay upright on teasing with a loop. In the *B. subtilis* group, colonies are large (2–7 mm) with a frosted-glass appearance but may become opaque on blood agar with β hemolysis. Variable colonial morphology is seen as some species may produce mucoid or smooth or raised wrinkly colonies.

Species differentiation of the genus is complex and, in some instances in a routine laboratory, a combination of Gram stain and colonial appearance, motility, and biochemical identification using commercial automated microbial identification system, like API kits or ViTEK (bioMérieux), machine using BCL cards [28]. Identifications are made after 14 h incubation, and the database allows for identification of up to 46 species. Recently, matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF MS) is being applied for identification of species, and this is based on the protein composition of a bacterial cell. This technique is also has also been found to be a good alternative to 16S rRNA sequencing and even a more powerful tool in the accurate classification of *Bacillus* species, especially for differentiating *B. subtilis* and *B. cereus* from *Bacillus*

amyloliquefaciens and *Bacillus thuringiensis*, respectively [29]. However, further studies are still required to test this technology with a large collection of *Bacillus* of diverse origins. A variety of other rapid identification methods have been developed for isolates from clinical samples which include molecular techniques such as pulsed field gel electrophoresis (PFGE), multilocus sequence typing (MLST), and 16S rRNA gene sequencing [30]. While all of these approaches enable subtyping of strains, they remain accessible to reference laboratories only and are difficult to implement for routine bacterial identification in a clinical laboratory.

Treatment Outcomes

Bacillus infections are rapidly spreading and destructive; the overall visual and anatomic outcomes are poor. In the largest series reported thus far by Das et al. [21], half of the patients regained ambulatory vision and over 40% developed phthisis bulbi. In a previously reported large series of ten cases, five cases needed enucleation due to panophthalmitis, and of the remaining, three had just light perception or less vision at the last follow-up [31]. The treatment outcome in two large series from the LV Prasad Eye Institute is shown in Table 20.2. The outcome of *Bacillus* endophthalmitis continues to be dismal.

Table 20.2 Comparison of clinical features of *Bacillus* endophthalmitis at LV Prasad Eye Institute one decade apart

		Das et al. [21] $n = 31$			Dave et al. [26] $n = 86$		
Presenting vision	Outcome	Gp A	Gp B	Gp C	Gp A	Gp B	Gp C
	LP	12 (38.7%)	3 (9.6%)	14 (45.1%)	24 (27.9%)	35 (40.6%)	11 (12.7%)
	≥FCF	1 (3.2%)	0	1 (3.2%)	3 (3.4%)	7 (8.1%)	6 (6.9%)
Time to surgery	Outcome	Gp A	Gp B	Gp C	Gp A	Gp B	Gp C
	<7 days	4 (12.9%)	1 (3.2%)	5 (16.1%)	0	1 (1.1%)	3 (3.5%)
	≥7 days	9 (29.0%)	2 (6.4%)	10 (32.2%)	27 (31.3%)	41 (47.6%)	14 (16.2%)
Microbiology	Outcome	Gp A	Gp B	Gp C	Gp A	Gp B	Gp C
	Bacillus only	7 (22.5%)	2 (6.4%)	12 (38.7%)	24 (27.9%)	35 (40.6%)	16 (18.6%)
	Polymicrobial	6 (19.3%)	1 (3.2%)	3 (9.6%)	3 (3.4%)	7 (8.1%)	1 (1.1%)

Group A, phthisical eye; eyes with no light perception
Group B, structurally preserved globe (intraocular pressure 5 mmHg) and best-corrected visual acuity ≤20/400
Group C, best-corrected visual acuity ≥20/400
FCF finger counting close to face, *LP* light perception

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Part III
Science of Endophthalmitis Treatment: Pharmacology

Chapter 21
Intravitreal Antibiotics

Sharat Hegde and Avinash Pathengay

Intravitreal antibiotic is the current standard of care in infectious endophthalmitis of any cause. The vitreous is a transparent gelatinous avascular body rich in collagen and hyaluronic acid; it provides a good culture medium for microorganisms to proliferate. In order to eliminate infection in endophthalmitis, antibiotics must reach the intraocular space and adjacent ocular tissues in adequate levels so as to reach above the minimum inhibitory concentration (MIC). Static and dynamic ocular barriers (blood-ocular barrier) that form a part of natural protective mechanisms of the eye impede the penetration of systemically and topically administered antibiotics.

Various factors are responsible for poor penetration of topical and systemic antibiotics: The tear film dilutes topically instilled medicines [1]. Low molecular weight drugs undergo systemic absorption from the conjunctival capillaries, and hence, bioavailability decreases [2]. Tight junctions in corneal epithelium lead to poor paracellular drug penetration especially for ionic drugs [3]. Systemically administered drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the intraocular space via the retinal pigment epithelium (RPE) impedes the further access into the ocular cavity [4]. An intravitreal injection bypasses the blood-retinal barrier as drug is injected directly into the vitreous cavity. Thus, antibiotics delivered through the intravitreal route achieve a higher drug concentration for prolonged periods of time [5].

History of Intravitreal Antibiotics

Injection of intravitreal antibiotics dates back to around 1940s when Sallmann et al. injected penicillin in a rabbit eyes with traumatic endophthalmitis [6]. Intravitreal antibiotic era was heralded when Peyman and associates (1970s) conducted

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experimental studies on endophthalmitis-induced rabbits and established the recommended doses of various intravitreal antibiotics [7, 8]. Later, many experimental studies were conducted on small animals and nonhuman primate models to establish the mechanisms of drug clearance and safety doses of intravitreal antibiotics [9]. The class of drug, mechanism of action, and susceptible organisms to the antimicrobials are mentioned in Table 21.1.

Table 21.1 Class of drug, mechanism of action, and susceptibility of the commonly used antimicrobials in endophthalmitis

Drug	Class of drug	Mechanism of action	Susceptible organisms
Amikacin	Aminoglycoside	Inhibits protein synthesis by binding to 30S subunit of ribosomes	Aerobic GNBs, *Pseudomonas aeruginosa*
Amphotericin B	Polyene antibiotics	Binds to ergosterol and alter the permeability of the cell wall	Yeasts, filamentous fungi (resistance for various species of *Aspergillus)*
Ceftazidime	Third-generation cephalosporin	Inhibits peptide cross-linking of polysaccharide chains of peptidoglycan; affects cell wall synthesis	Aerobic GNBs, GPBs including *Pseudomonas*
Cefazolin	First-generation cephalosporin	Inhibits peptide cross-linking of polysaccharide chains of peptidoglycan; affects cell wall synthesis	GPC, GPB, *E. coli*, *Proteus*, *H. influenzae*
Ciprofloxacin	Fluoroquinolones	Topoisomerase II inhibitors (DNA gyrase)	Broad-spectrum activity against aerobic gram-positive and gram-negative bacteria, *Actinomyces*, *Nocardia* sp.
Imipenem	Carbapenem	Inhibits cell wall synthesis, prevents cross-linking of peptidoglycan during cell wall synthesis	MDR GPB, GNBs including *Pseudomonas aeruginosa*, therapeutic option for infections caused by MDR pathogens
Piperacillin/ tazobactam	Beta-lactam antibiotics	Inhibit cell wall synthesis, binding to penicillin-binding proteins	GNBs, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*; therapeutic option for infections caused by MDR pathogens
Vancomycin	Glycopeptide	Inhibits the synthesis of precursor units of bacterial cell wall; inhibits RNA synthesis	GPC—MRSA and MDR *Staphylococcus epidermidis*
Voriconazole	Triazoles	Inhibition of ergosterol synthesis which increases membrane permeability	Broad-spectrum activity against molds and yeasts

GPC Gram-positive cocci, *GPB* gram-positive bacilli, *GNB* gram-negative bacilli, *GNC* gram-negative cocci, *MDR* multidrug resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*, *VRSA* vancomycin-resistant *Staphylococcus aureus*

Ocular Factors Influencing Intravitreal Antibiotics

Intravitreal injection bypasses the various anatomical and physiological ocular barriers and diffuses freely in the vitreous cavity to reach the retinal surface. The following factors influence the drug distribution, concentration, and clearance from the vitreous cavity [10]:

1. Route of exit: large molecules like vancomycin, aminoglycosides, and macrolides are known to leave the eye predominantly by the passive diffusion through the anterior chamber, while small molecules such as beta-lactams, clindamycin, and fluoroquinolones are cleared by active transport via the blood-retinal barrier [11] (Fig. 21.1).
2. Ionic nature: anionic drugs like beta-lactams, cephalosporins, and clindamycin primarily undergo clearance rapidly via the posterior route across the blood-retinal barrier, while cationic drugs like vancomycin, aminoglycosides, and erythromycin have a comparatively longer half-life as they undergo clearance by passive diffusion into the aqueous and exit via the anterior chamber [9, 12, 13]. Fluoroquinolones which are zwitterions have the shortest half-life as they are cleared via both anterior and posterior routes (Fig. 21.2) [14, 15].

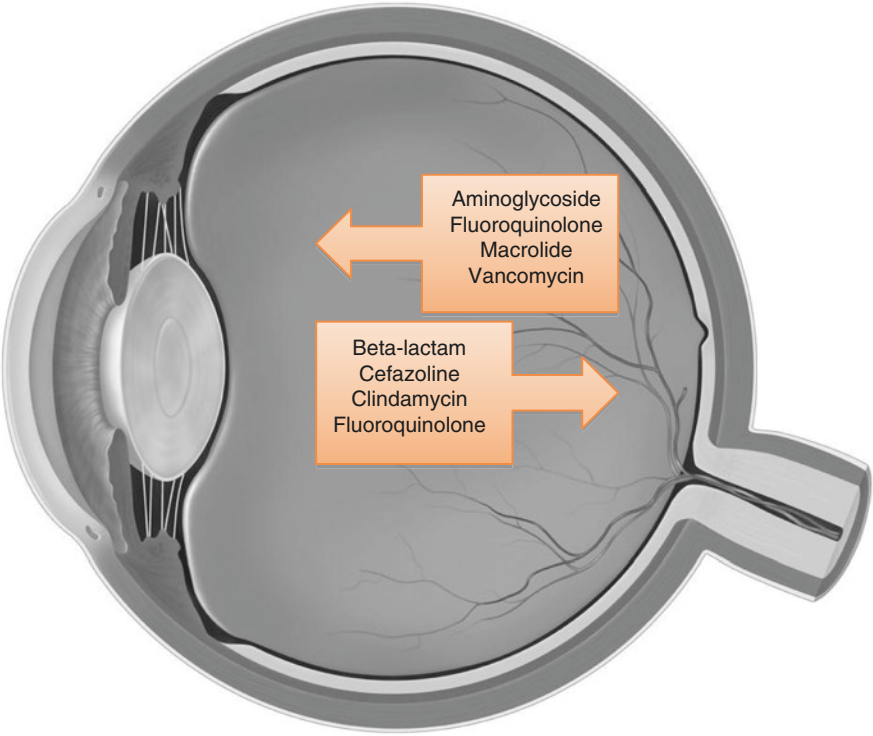

Fig. 21.1 Common antibiotic clearance from the eye

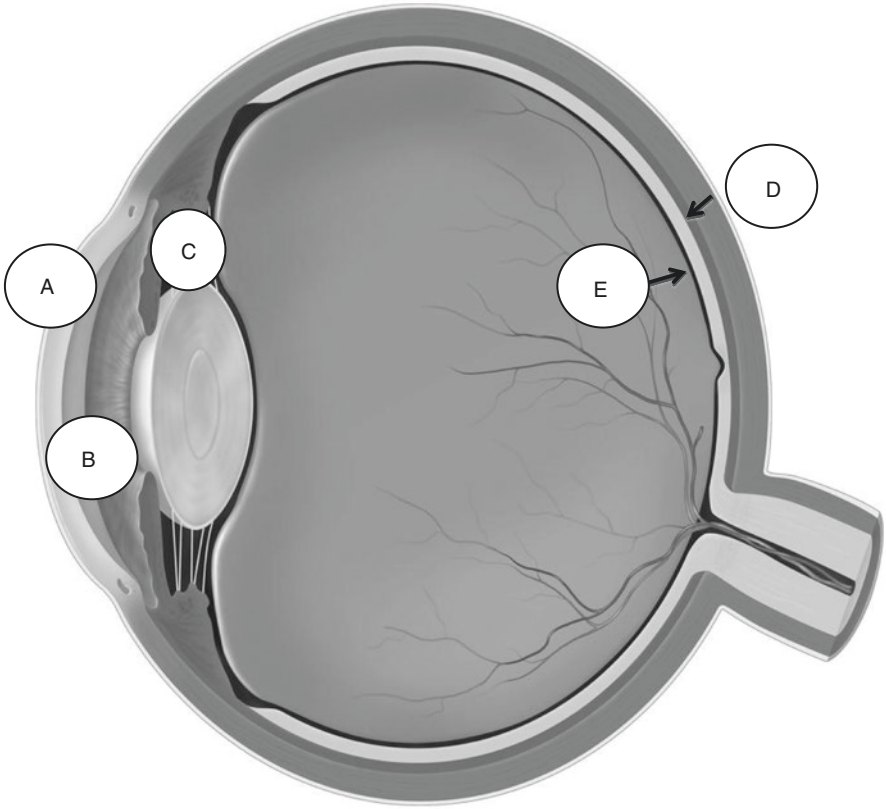

Fig. 21.2 Depicting the routes of exit for various intravitreal antibiotics. (*a*) Epithelial barrier, (*b*) aqueous-vitreous barrier, (*c*) blood-aqueous barrier, (*d*) outer retinal barrier, (*e*) inner retinal barrier (Adapted from Cunha Vaz JG, et al. Doc Ophthalmol 1997; 93:149–57)

3. Solubility coefficient of the drug: lipophilic antibiotics like fluoroquinolones and chloramphenicol are cleared by passive diffusion, while water-soluble antibiotics like beta-lactams leave the eye via active transport [9, 12].
4. Status of ocular inflammation: In an inflamed eye, the drug clearance through the anterior route is faster, while the clearance via the posterior route is delayed due to a compromise RPE pump. Thus in an inflamed eye, antibiotics that are routinely eliminated through the anterior route are cleared faster, while the drug clearance by the posterior route is retarded, thus increasing their half-life [9, 13, 16–18].
5. Surgical status of the eye: In aphakic eyes, the clearance of antibiotics that leave the eye through the anterior route is fast, while in vitrectomized eyes the drugs that leave via the posterior route are increased. In an experimental study, retinal toxicity to routinely used doses of intravitreal antibiotics in silicone oil-filled eyes was noted. This was due to confinement of the drug in the reduced preretinal space causing its delayed clearance [19].

6. Molecular weight: the retention of the drug in the vitreous cavity increases with its increase in molecular weight as it becomes relatively impermeable to the blood-retinal barrier. As most drugs have a molecular weight of <500 Da, their half-life is <72 h [17].
7. Vitreous liquefaction: the half-life of the drug is reduced in presence of liquefied vitreous in the anterior and posterior few millimeters of the globe [17].
8. Solution density: If the density of the injected solution is greater than vitreous, it may settle down with gravity and cause localized retinal toxicity. To avoid this complication, intermittent repositioning of the patients head is required [20].
9. Frequency of intravitreal antibiotic administration: The need for repeated intravitreal antibiotic injection depends on the clinical response, half-life of the drug, and surgical status of the eye. The aim of repeat dosing is to maintain the drug concentrations above the MIC, rather than to attain higher peak levels. Thus, adequate and safe antibiotic levels can be better achieved by frequent rather than higher dosages [16].

Intravitreal Antibiotic Dose

The efficacy of intravitreal antibiotics is based on the duration the intraocular drug level exceeds the MIC of a particular drug against the implicated organism. The safe and therapeutic intravitreal doses of commonly used antibiotics have been determined in experimental and clinical studies. The recommended doses and frequency of repeated injections have been mentioned in Table 21.2.

Preparation of Intravitreal Antibiotics

According to various experimental and clinical studies, the recommended therapeutic dosage of intravitreal antibiotics is very small compared to its systemic dosing and is carefully titrated to prevent retinal toxicity. Thus, it is important that an accurate dose is maintained each time an injection is prepared [21]. The injections should be prepared following standard protocols by trained personnel under strict aseptic conditions in a certified laminar flow area. Also a printed drug preparation reference display sheet should be consulted while preparing injections to prevent dilution errors. Preparation of important intravitreal antibiotics is shown in Table 21.3. Though the expiry of various drugs prepared for intavitreal use is not known, an experimental study reported that vancomycin, ceftazidime, and moxifloxacin when prepared in single-use polypropylene syringes and stored at −20 °C or −80 °C retain their potency, sterility, and stability up to 24 weeks [22].

Table 21.2 Pharmacokinetics of intravitreal antimicrobials: dose, route of exit and half-life in non-vitrectomized and vitrectomized eyes, and frequency of repeated injections

#	Drug	Recommended dose (μg/0.1 ml)	Route of clearance	Half-life ($t_{1/2}$) in vitreous Noninflamed phakic eyes	Aphakic vitrectomized eyes	Frequency of repeat injections (h)
1	Amikacin [25, 49, 50]	400	Anterior	25.5 h	NA	24–48
2	Amphotericin-B [51]	5–10	Posterior	8.9 days	1.8 h	NA
3	Aztreonam [52]	100	Posterior	7.5 h	NA	12
4	Cefazolin [9, 21]	2	Posterior	6.5 h	NA	24
5	Ceftazidime [25, 53]	2	Posterior and anterior	13.8 h	NA	48–72
6	Ciprofloxacin [14, 16]	100	Anterior and posterior	3.5–5.5 h	1.2 h	12
7	Clindamycin [54]	1000	Posterior	40 h	NA	72
8	Daptomycin [55]	200	Posterior	42 h	NA	Single dose
9	Dalfopristin/quinupristin [56]	400	Posterior	NA	NA	48
10	Gentamicin [57, 58]	100	Anterior	40–60 h	<40 h	72–96 h
11	Imipenem [59]	50–100	Posterior	NA	NA	NA
12	Linezolid [60, 61]	400	NA	2 h	NA	NA
13	Moxifloxacin [12]	200	Anterior and posterior	1.72 h	NA	12
14	Ofloxacin [15]	200–500	Anterior and posterior	5.6 h	NA	24
15	Penicillin [6]	2–4000 units	Posterior	NA	NA	48
16	Piperacillin/tazobactam [26–28]	225 <250	Posterior	NA	NA	NA
17	Sulfamethoxazole/trimethoprim [12]	1600 trimethoprim	Anterior	NA	NA	NA
18	Vancomycin [13]	1000	Anterior	25.5–56 h	9.8 h	72
19	Voriconazole [62]	50–200	Posterior	2.5–6.5 h	NA	NA
20	Meropenem [63]		Posterior	2.6 h	NA	NA

Table 21.3 Preparation of intravitreal antibiotics

#	Injection	Add distilled water	Take	Add to Ringer's lactate	Dosage in 0.1 ml
	Antibacterial antibiotic				
1	Amikacin 100 mg		0.1 ml	0.9 ml	400 μg
2	Cefazolin 500 mg	2 ml	0.1 ml	0.9 ml	2.25 mg
3	Ceftazidime 250 mg	1 ml	0.1 ml	0.9 ml	2.25 mg
4	Imipenem 500 mg	NS 10 ml	0.1 ml	0.9 ml double dilution	50 μg
5	Piperacillin and tazobactam 4.5 mg	20 ml	0.1 ml	0.9 ml double dilution	225 μg
6	Vancomycin 500 mg	10 ml	0.2 ml	0.8 ml	1 mg
	Antifungal antibiotics				
7	Amphotericin-B 50 mg	10 ml	0.1 ml	0.9 ml double dilution	5 μg
8	Voriconazole 200 mg	20 ml	0.1 ml	0.9 ml	100 μg

Activity Spectrum and Choice of Antibiotics

Prompt and early clinical, therapeutic, and diagnostic decisions have to be made in cases of endophthalmitis. The initial decision is based on the presenting history and clinical examination and is often empirical, without access to any laboratory or culture results. Ideally an empirical antibiotic combination should cover most common and possible causative agents. Bactericidal agents are preferred over bacteriostatic agents as the eye is an immune-privileged site. The commonly used empirical antibiotic regimen is vancomycin plus ceftazidime or amikacin. Vancomycin is effective against most gram-positive cocci; ceftazidime and amikacin are effective against most gram-negative bacilli. The endophthalmitis vitrectomy study (EVS) used the combination of vancomycin and amikacin though [23] the final recommendation was to use ceftazidime because of reported retinal toxicity of amikacin [24]. The choice of antibiotic can be further modified based on sensitivity spectrum.

The emergence of multidrug-resistant bacteria causing endophthalmitis is a matter of concern in India. Alternative antibiotics like imipenem or fluoroquinolones may be considered for the management of these resistant organisms [25]. In recent times, intravitreal piperacillin-tazobactam has been studied both in animal models and clinically; it is considered a useful alternative to ceftazidime [26–28].

Frequency and Safety of Repeated Intravitreal Injections

Repeat antibiotic injections are required in few circumstances—in persistent endophthalmitis and in fungal endophthalmitis [29]. Decision to repeat intravitreal antibiotic depends on subjective assessment of clinical response, microbiological

results, and toxicity of the chosen drugs. The aim of repeat dosing should be to optimize the duration of drug exposure concentration above the MIC [30, 31]. Retreatment with intravitreal antibiotics with or without vitrectomy should be considered when the treated eye is not stable/not improved after first 36–48 h or there are signs of worsening. Choice of repeat antibiotics should be guided by culture and sensitivity results of vitreous or aqueous tap.

Combination of Drugs

The ideal drug must show a good antibacterial activity against both gram-positive and gram-negative organisms, without being toxic for ocular structures, particularly the retina. Presently, no single antibiotic covers efficiently all organisms that cause endophthalmitis; a combination of at least two drugs is thus required. The practice of combining two drugs for treatment of bacterial endophthalmitis is aimed to provide a broad-spectrum cover for both gram-positive and gram-negative organisms [32]. The most commonly used combination is vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml) or amikacin (0.4 mg/0.1 ml) [33]. Imipenem can also be used with vancomycin as combination therapy in case of fulminant endophthalmitis [25].

Combining drugs may also influence the pharmacokinetics of the drugs. Studies have shown that ceftazidime and vancomycin precipitate if taken in the same syringe [33, 34] but do not lose potency of either antibiotic [35]. There is one report suggesting that adding intravitreal dexamethasone decreases the elimination time of vancomycin in inflamed eyes by stabilizing the blood-retinal barrier [36].

Antibiotic Resistance

Indiscriminate and injudicious use and abuse of antibiotics has led to development of resistant bacterial strains among both ocular and nasopharyngeal flora, as well as pathogenic organisms. Endophthalmitis caused by these organisms is associated with a stormy clinical course and worse visual outcomes [22, 37, 38]. Emerging resistance of organisms to standard antibiotic therapy needs continuous evaluation for the ideal intraocular antibiotics. In such situation, choice of antibiotics is judiciously guided by culture result and sensitivity patterns of the causative organism. But it is also known that resistance found in vitreous does not always correlate with clinical resistance and routinely administered antibiotic doses provide intraocular drug concentration higher than the MICs of most pathogens [37, 38]. A good knowledge of the pharmacokinetics and pharmacodynamics of drug, infection site, and MIC is needed to properly predict in vivo efficacy of antibiotics against target pathogen [39].

Future Trends

A few important factors that increase the therapeutic efficacy of the drug are patient compliance and comfort during drug administration. This can be achieved by various advances in ocular drug delivery such as improved drug bioavailability, prolonged duration of drug action, higher efficacy, improved safety, and less invasive administration [40].

A prodrug is defined a biologically inactive compound which can be metabolized in the body to produce an active drug, essentially in a single step (i.e., enzymatic conversion) [41]. For ocular use, intravitreally administered liposomes containing a lipid prodrug could significantly increase drug half-life and minimize the intraocular side effects of drugs. For example, intravitreal injection of liposomes containing a lipid prodrug of ganciclovir is shown to inhibit CMV retinitis in rabbits [42, 43]. Improvement in drug bioavailability is also seen in the mechanism of iontophoresis where applying an electrical current to an ionizable substance increases its mobility across a surface. A novel iontophoretic system, the EyeGate II Delivery System (EGDS; EyeGate Pharmaceuticals, Inc., Waltham, MA, USA), is designed to achieve optimal therapeutic levels of drug in the eye while simultaneously minimizing systemic distribution [44, 45].

Controlled-release drug delivery in the form of nanoparticles helps in increasing the efficacy and prolonging the duration of drug action. These nanoparticles consist of various biodegradable materials, such as natural or synthetic polymers, lipids, phospholipids, and metals. Studies have shown that nanoparticles of different sizes and electric charges, when injected into the vitreous, migrate through the retinal layers and tend to accumulate in the RPE cells up to 4 months after a single intravenous injection [46]. Also drug delivery systems in the form of nonbiodegradable and biodegradable devices or implants have been investigated [41, 47, 48].

Pharmacokinetics, safety, and efficacy of newer antibiotics and antifungals must be continually explored in view of the emerging multidrug and sometimes pan-drug resistance among organisms causing ocular infections.

Frequently Asked Questions

1. *Which is the most effective modality of antibiotic administration in endophthalmitis?*
   A: Antibiotics in the management of endophthalmitis are administered through three routes—the topical, systemic, and intravitreal. Of these three routes, intravitreal antibiotics provide 10–100-fold concentrations in vitreous; it is greater than MIC level of most organisms. Systemic antibiotics could provide concentration above MIC levels (not as high as intravitreal drug) in vitreous, but it is delayed by 2–3 days. Topical antibiotics fail to reach desired MIC level in the vitreous cavity.

2. *How to select empirical antibiotics in the management of endophthalmitis?*
   A: The need for empirical antibiotics arises because clinical evaluation usually cannot differentiate gram-positive from gram-negative infection. Hence, antibiotics that cover both gram-positive and gram-negative organisms have to be considered for effective management of bacterial endophthalmitis. Additional factors that guide us in selection of these antibiotics include:

   (a) Susceptibility pattern of the bacteria
   (b) Pharmacokinetics of intravitreal antibiotics
   (c) Safety profile of the antibiotics
   (d) Efficacy of the antibiotics

   It is important that every laboratory checks the antibiotic sensitivity of the bacteria causing endophthalmitis; this is the proven way to decide whether to continue or substitute the preinjected antibiotics in the management of endophthalmitis.

3. *When should one repeat intravitreal antibiotics?*
   A: Many times single intravitreal administration of antibiotics may be sufficient in the management of endophthalmitis; there could be certain situation where same or different antibiotics are repeated more than once. These situations include:
   (a) Persistent endophthalmitis
   (b) Recurrent endophthalmitis
   (c) Slow-growing organisms like fungus and mycobacteria
   (d) Resistance to the injected antibiotics

   Care must be taken to understand the pharmacokinetics of intravitreal drugs to prevent drug toxicity due to reinjection.

4. *What is the dose of intravitreal antibiotics in silicon-filled eyes?*
   A: Low concentration, such of one-fourth of the concentration of the antibiotics, is injected over the preretinal surface following which the silicone oil is injected. This concentration is preferred to avoid possible drug-related toxicity.

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Chapter 22
Corticosteroids in Endophthalmitis

Shreyansh Doshi and Avinash Pathengay

Endophthalmitis is a rare but serious complication of any intraocular procedure, penetrating eye trauma and occasionally haematogenous spread of an infective organism from a distant focus. The outcome of bacterial endophthalmitis depends on multiple factors such as virulence and load of the organism, the duration between onset of infection and initiation of treatment, condition of the eye at presentation, type and route of antibiotic administration, patient age and immunity status [1]. The virulent organisms release toxins and tissue- damaging enzymes which persist even after sterilization of the intraocular space with antibiotics [2]. The host inflammatory response may also be responsible for retinal destruction and permanent visual loss. These two factors may account for treatment failure as the persistent intraocular inflammation provides a scaffold for formation of the epiretinal and vitreal membranes which further worsen the prognosis [3].

Histopathologic studies of ocular tissues following endophthalmitis have shown that infections with cytotoxic bacterial strains lead to substantial damage to retinal cells, while non-cytotoxic bacterial strains lead to an infiltration of immune cells in the vitreous cavity leaving the retina structurally intact [4]. Thus, the suppression of this inflammatory component and restoring the blood-ocular barrier by an anti-inflammatory agent like corticosteroids may result in preservation of the retinal architecture and result in a better visual outcome [5, 6]. The arguments against the use of corticosteroids involve possible corticosteroid-induced toxicity, blunting of the immune response that is necessary to combat bacterial infection and decreased concentrations of vitreous antibiotics [7, 8].

Multiple advances have been made in the treatment of endophthalmitis in the last two decades beginning with the Endophthalmitis Vitrectomy Study (EVS) [9]. The EVS recommended intravitreal antibiotics with vitrectomy (for eyes with presenting vision less than hand motions) or vitreous tap (for eyes with presenting hand motion vision or more). The EVS treated the patients with oral corticosteroid a day after the

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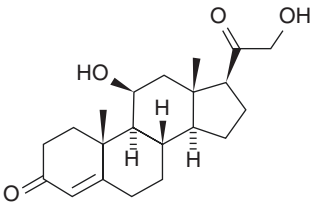

Fig. 22.1 Structure of corticosteroid

intravitreal antibiotics, but not with intravitreal steroid. There is no consensus regarding the role of corticosteroids such as oral prednisolone, intravitreal dexamethasone or intravitreal triamcinolone acetonide in the treatment of endophthalmitis.

Chemical Structure

Corticosteroids (glucocorticoids and mineralocorticoids) are 21-carbon structures that are synthesized from cholesterol by adrenocorticotropic hormone in the adrenal cortex (Fig. 22.1). Natural forms such as cortisol, cortisone, corticosterone or aldosterone can be formed in the adrenal cortex, while many synthetic forms like prednisone, methylprednisolone, dexamethasone, triamcinolone and betamethasone are also available.

Mechanism of Action

Corticosteroids exert their anti-inflammatory activity through the following mechanisms:

- They cause constriction of blood vessels, which reduces the vascular permeability, thereby reducing leakage of fluid, proteins and inflammatory cells into the target site [10].
- Corticosteroids prevent adherence of neutrophils to the vascular endothelium, thus decreasing their mobility and making them less accessible to the site of inflammation [11].
- They stabilize intracellular lysosomal membranes and inhibit the expression of various damaging enzymes [12].
- Stabilization of mast cell and basophil membranes by corticosteroids plays an important role in inhibiting the process of degranulation and further release of inflammatory mediators [12].
- Corticosteroids inhibit macrophage recruitment and migration and also interfere with the ability of macrophages to process antigens [13].
- Corticosteroids inhibit phospholipase A2 resulting in inhibition of arachidonic acid degradation. Thus, subsequent synthesis of prostaglandins and leukotrienes by cyclooxygenase and lipoxygenase pathways is affected [14].

Role of Mineralocorticoids in Inflammation

Aldosterone is a mineralocorticoid receptor agonist which can be expressed by cells of the immune system and has been associated with release of proinflammatory cytokines, generating oxidative stress and inducing fibrosis [15]. Normally, in the body, mineralocorticoid receptor is co-expressed with 11β-hydroxysteroid dehydrogenase 2 enzyme, which converts active cortisol into inactive glucocorticoids. The close proximity of this enzyme and mineralocorticoid receptor has been proposed to prevent the receptor activation by glucocorticoids [16, 17].

Under physiological conditions, the circulating glucocorticoid concentrations are 100–1000 times higher than those of aldosterone. Thus, the mineralocorticoid receptor activity is most likely controlled by glucocorticoids and not aldosterone [18]. To avoid the adverse effects caused by excessive mineralocorticoid receptor action, synthetic glucocorticoids have been designed to activate glucocorticoid receptor only and not the mineralocorticoid receptor. These drugs are widely used in therapy of inflammatory and autoimmune diseases [19, 20].

The general therapeutic effects in different organs of the body and side efffects of glucocorticoid are shown in Fig. 22.2.

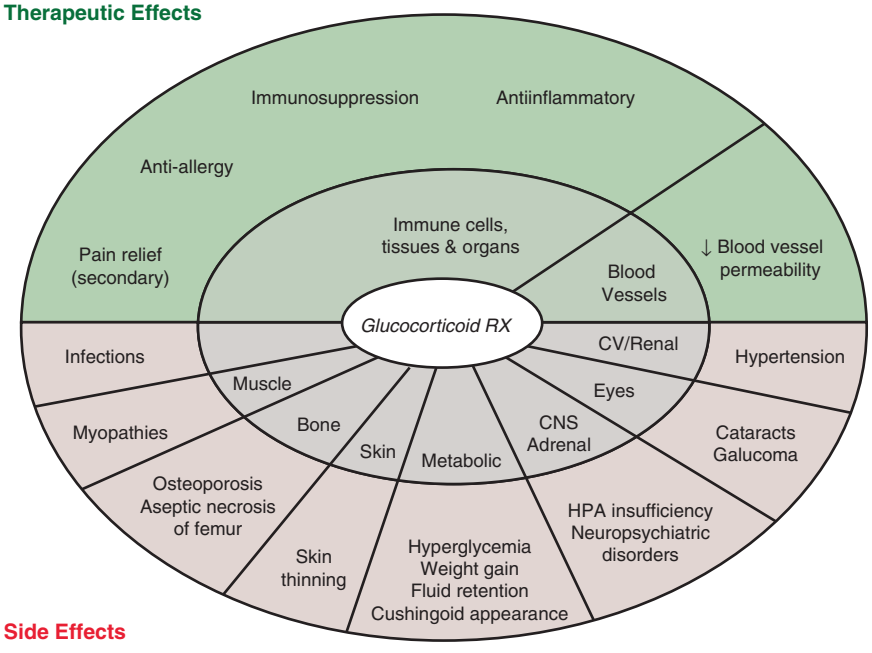

Fig. 22.2 Therapeutic and side effects of glucocorticoid

Dose and Route of Administration of Corticosteroids in Endophthalmitis

Intravitreal Route

Dexamethasone is the most common steroids administered intravitreally. Intravitreal dexamethasone has been proven nontoxic in rabbits up to 400 μg, but there is no precise minimum dose for the therapeutic effect, and even the smallest dose has some beneficial effect [21]. In a prospective randomized trial, it was reported to reduce inflammation faster both in culture-positive and culture-negative endophthalmitis and did not affect the final visual outcome [22]. It is advisable to inject intravitreal steroids separately and not with other antibiotics, particularly vancomycin, since precipitation of the drug is known to occur.

Topical

Topical steroids have the potential to penetrate an intact cornea and its efficacy is proportional to the frequency of instillation [23].

Systemic Route

It is a general practice to withhold the administration of systemic steroids until the culture reports are available and specific antibiotics are administered for at least 24 h. The recommended dose is 1.0–1.5 mg/kg/day of oral prednisolone administered in two to three divided doses to achieve uniform concentration throughout the day [23].

While most ophthalmologists agree that steroids have a potentially beneficial role in bacterial endophthalmitis, the choice of the route of administration is not uniform with most controversies persisting in regard to the intravitreal steroid therapy.

Timing of Intravitreal Steroid Injection

The combination therapy of antibiotic and dexamethasone given between 24 and 72 h after inoculation reduced inflammation in *Staphylococcus aureus* endophthalmitis in rabbits [24, 25], though it did not work in experimental *Pseudomonas* endophthalmitis when the combination therapy was given 6 h after the inoculation [21, 26]. While there are multiple studies indicating the timing of the first corticosteroid intravitreal injection, there is no study on the effect of repeated intravitreal corticosteroids in endophthalmitis.

Choice of Corticosteroids

Triamcinolone Acetonide

Triamcinolone is a synthetic corticosteroid (Fig. 22.3) and is eight times more potent than prednisolone. Triamcinolone seems to contain inflammation in experimental *Staphylococcus* endophthalmitis [27, 28]. Safety and efficacy have been shown in human studies [5, 29] when given after the sensitive intravitreal antibiotic injection. Triamcinolone acetonide is a suspension; it is given at a dose of 4 mg in 0.1 ml, and the clearance time in rabbit is faster in vitrectomized eyes (1.57 day in vitrectomized eyes and 2.89 in non-vitrectomized eyes) [30].

Dexamethasone Sodium Phosphate

Dexamethasone sodium phosphate (Fig. 22.4) is a clear solution. The intravitreal dose is 0.4 mg in 0.1 ml, and its half-life is quite short. While in a prospective human study involving 63 patients Das et al. [22] have shown quick reduction in inflammation without affecting the final vision at 3 months, Shah et al. [7] in a retrospective study involving 57 patients reported less likelihood of three lines of improvement in eyes that received intravitreal dexamethasone as part of endophthalmitis management [7]. Subsequent studies by Gan et al. [31] and Albrecht et al. [32] did not report any adverse impact of intravitreal dexamethasone adjuvant therapy on the final visual outcome in human eyes.

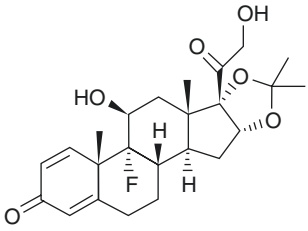

Fig. 22.3 Structure of triamcinolone acetonide

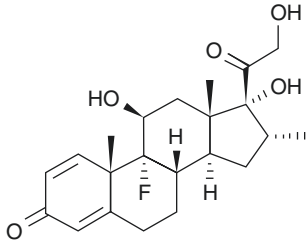

Fig. 22.4 Structure of dexamethasone

Intravitreal corticosteroids are not advocated in fungal endophthalmitis. Majji et al. [33] did not report any detrimental effect of intravitreal dexamethasone given to eyes as part of a larger prospective study; in fact, the number of patients with favourable visual outcome was greater in the corticosteroid group. In an experimental study, *Candida albicans* endophthalmitis, when treated with a combination of amphotericin B and dexamethasone intravitreal injection, resulted in clearer vitreous and did not compromise the antifungal effect of amphotericin B [34].

The clinical and experimental studies of intravitreal corticosteroid are shown in Tables 22.1 and 22.2.

Effect of Intravitreal Corticosteroids on Vitreous Antibiotic Concentrations

There are a few studies on the effect of dexamethasone on the vancomycin level in the vitreous cavity. Smith et al. in an experimental methicillin-resistant *Staphylococcus epidermidis* endophthalmitis in rabbits reported increased elimination but suspected that it could be because of vancomycin and dexamethasone precipitation when given together [8, 44]. Others, Park et al. [45] and Gan et al. [46], have reported higher vancomycin level in rabbit vitreous in presence of dexamethasone.

Table 22.1 Studies involving intravitreal corticosteroids in endophthalmitis in human subjects

Author	Intravitreal steroid	Organism	Result
Das et al. [22]	Dexamethasone	Bacteria	Early reduction of inflammation but no change in final visual outcome in steroid-antibiotic combination group
Shah et al. [7]	Dexamethasone	Bacteria	Reduced likelihood of obtaining a three-line improvement in visual acuity in steroid-antibiotic combination group vs. antibiotic alone group
Gan et al. [31]	Dexamethasone	Bacteria	Better visual outcome in steroid-antibiotic combination group vs. placebo and antibiotic
Albrecht et al. [32]	Dexamethasone	Bacteria	Steroid group had better visual acuity compared to the placebo, but this was not statistically significant
Majji et al. [33]	Dexamethasone	Fungi	Favourable visual outcome was greater in the steroid antifungal combination group, but this was not statistically significant
Flak et al. [29]	Triamcinolone acetate	Bacteria	Favourable outcome in steroid-antibiotic combination group
Pathengay et al. [5]	Triamcinolone acetate	Bacteria	Reduced inflammation in steroid-antibiotic combination group

Table 22.2 Studies involving intravitreal corticosteroids in experimental endophthalmitis in rabbits

Author	Intravitreal steroid	Organism	Result
Yoshizumi et al. [24]	Dexamethasone	*Staphylococcus aureus*	Group treated with steroid-antibiotic combination showed better ERG response and less inflammation
Ermis et al. [35]	Dexamethasone	*Staphylococcus aureus*	Difference in the histopathological scores between the treated groups was not statistically significant
Meredith et al. [36]	Dexamethasone	*Staphylococcus aureus*	Group treated with intraocular steroids showed increased inflammatory scores, choroidal inflammation and retinal necrosis
De Kaspar et al. [25]	Dexamethasone	*Staphylococcus aureus*	Group treated with steroid-antibiotic combination showed better ERG response and less clinical and histological inflammation
Yildirim et al. [37]	Dexamethasone	*Staphylococcus epidermidis*	Lower histopathological scores in treated groups vs. control groups
Smith et al. [8]	Dexamethasone	*Staphylococcus epidermidis*	Less histological inflammation in group treated with steroid-antibiotic combination
Meredith et al. [38]	Dexamethasone	*Staphylococcus epidermidis*	Quantitative grading of inflammation and media clarity was least in the group treated with vitrectomy, intraocular antibiotics and steroids
Ermis et al. [39]	Dexamethasone	*Staphylococcus epidermidis*	Difference in the histopathological scores between the treated groups was not statistically significant
Park et al. [2]	Dexamethasone	*Streptococcus pneumoniae*	Significant reduction in intraocular inflammation in the steroid-antibiotic combination treated group
Liu et al. [40]	Dexamethasone	*Bacillus cereus*	Significant decreased inflammation in the retina was seen in the steroid-antibiotic combination group
Liu et al. [40]	Dexamethasone	*Bacillus cereus*	Histopathologically less conjunctival inflammation, iritis, choroidal vasculitis and retinitis in the steroid-antibiotic combination group

(continued)

Table 22.2 (continued)

Author	Intravitreal steroid	Organism	Result
Wiskur et al. [41]	Dexamethasone	*Bacillus cereus*	Steroid-antibiotic combination did not provide any additional benefit, and steroids reduced the efficacy of intravitreal antibiotics
Pollack et al. [42]	Dexamethasone	*Bacillus cereus* exotoxin	Compared to controls, intravitreal steroid injection did not appear to attenuate the intraocular inflammation
Graham et al. [21]	Dexamethasone	*Pseudomonas aeruginosa*	Significant reduced intraocular inflammation in group treated with steroids and antibiotics
Kim et al. [26]	Dexamethasone	*Pseudomonas aeruginosa*	In the early phase, intraocular steroid-antibiotic combination had no additional benefit compared to antibiotics alone
Jett et al. [43]	Dexamethasone	Cytolytic toxin producing *Enterobacter faecalis*	No difference in the course of disease between the treated group and control group
Jett et al. [43]	Dexamethasone	Non-cytolytic *Enterobacter faecalis*	Significant improvement in steroid-antibiotic combination group with no loss in ERG b-wave
Coats et al. [34]	Dexamethasone	*Candida albicans*	Relatively clearer vitreous in steroid-antifungal combination treated group compared to only antifungal group
Hosseini et al. [27]	Triamcinolone acetate	*Staphylococcus epidermidis*	Reduced inflammation in steroid-antibiotic group compared to the other groups
Bucher et al. [28]	Triamcinolone acetate	*Staphylococcus epidermidis*	Reduced severity of vitritis in steroid-antibiotic combination treated group compared to other groups

Concerns of Intravitreal Steroid Injections in Endophthalmitis

Despite all the experimental and human studies, several concerns of intravitreal corticosteroid in endophthalmitis persist.

The concerns are:

- Sensitivity of organism to antibiotics must be confirmed prior to injecting intravitreal steroids.
- Flaring up of infection after intravitreal steroid injection.
- Dilution of intravitreal antibiotic dose and increased removal of antibiotics.
- Precipitation of intravitreal antibiotic.

- Timing of first and repeat intravitreal steroid injection.
- Choice of corticosteroid and dosage.

Frequently Asked Questions

1. *When would you inject intravitreal steroids in endophthalmitis?*
   A: Intravitreal steroids could be considered in all cases of bacteria endophthalmitis when the causative organism is identified and antibacterial sensitivity is performed. The intravitreal antibiotics must be given prior to or along with intravitreal steroids.
2. *When should one exercise caution while administering intravitreal steroids in endophthalmitis?*
   A: Endophthalmitis with an unknown causative organism and slow-growing organism like *Nocardia*, atypical *Mycobacteria*, etc., traumatic endophthalmitis, fungal endophthalmitis and endophthalmitis worsening despite appropriate antibiotic treatment.
3. *Do intravitreal corticosteroid injections alter the pharmacokinetics of intravitreal antibiotics?*
   A: Intravitreal steroids are known to alter the concentration of intravitreal antibiotics in experimental studies by binding or precipitation of the antibiotic resulting in a lower measurable level of antibiotics in the vitreous. But despite this, a therapeutic level of the antibiotic is maintained for many days following the intravitreal injection. Some studies have reported increase in the concentration of the intravitreal antibiotic when injected along with steroid.

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Chapter 23
Pharmacokinetics of Antimicrobials in Endophthalmitis

Thirumurthy Velpandian and Madhu Nath

Pharmacokinetic-pharmacodynamic (PK/PD) paradigm of a drug plays a critical role in determining the clinical outcome for the individual patient [1]. PK/PD of an antimicrobial drug is crucial. Apart from the outcome of the individual patient, emergence of resistance to the invading microbe is also a matter of concern. Unlike antimicrobial treatment for systemic skin and soft tissue infections, organs protected by blood-tissue barriers exhibit differential pharmacokinetics for antibiotic in prophylaxis and treatment. Drug transfer across the intact blood-ocular barriers is highly regulated by the presence of drug transporters [2]. They govern the ocular pharmacokinetics of antimicrobial agents in relationship with its dynamic properties [3]. Therefore, drug treatment for ocular infections is much complicated than it was originally thought.

Prophylactic use of antimicrobial therapy for ocular procedures is a serious concern when it is argued in terms of reducing the global threat of resistance to antimicrobials. A large meta-analysis did not show any good evidence for preoperative antibiotic prophylaxis. Rather, a strict maintenance of aseptic conditions for ocular surgical procedures remains the gold standard to prevent the infections [4]. However, the use of antibiotic prophylaxis is left to the choice of ophthalmologist in high-risk conditions. Use of antibiotics in infusion fluid during ophthalmic surgeries is often used as an antimicrobial prophylaxis in ocular surgeries [5–7]. But the validity of this practice, its ocular pharmacokinetics and impact on minimizing intraocular infections, requires further studies [8–10]. Although much of information is available about the ocular pharmacokinetics of antimicrobial agents in normal conditions, understanding the altered pharmacokinetics of antimicrobial agents through systemic and direct intravitreal routes during endophthalmitis is of interest to rationalize the treatment for a therapeutic outcome.

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Invasion and Microbial Growth in Endophthalmitis

The stage-by-stage understanding about the growth of microbes in the eye is of immense importance while modeling the pharmacokinetics and its related microbial kill (pharmacodynamic) correlation (PK/PD) of either systemic or intraocular administrations of antimicrobials [11]. Pathogen-dependent factors such as generation time, virulence, quorum sensing, microbial susceptibility for the antimicrobial agent, and the bacterial enzyme activity affecting vitreous matrix/ocular tissues determine microbial load and extent of ocular damage on time scale in endophthalmitis. The host-dependent factors such as nutrition supply, status of immune defense, and effective antimicrobial disposition in the eye (after initiating drug therapy) are the key components determining its clinical outcome in endophthalmitis (Fig. 23.1).

Callegan et al. [12] have documented the stagewise growth after the inoculation of known amount of *B. cereus*, *S. aureus*, and *E. faecalis*. An approximate doubling time is 15–30 min from the time of inoculation in the rabbit eye. In general, the organisms with lower doubling time would reach maximum microbial load in a shortest time in the eye. Innate immune response is the first line of defense for the invading microbe in the body. Callegan et al. [12] reported that *B. cereus* has a doubling time of 18–27 min and reaches stationary phase in 12 h time; this supports the argument that the microbe could freely replicate, produce toxins, and damage tissues in an immune-privileged environment of the eye. Although the direct correlation

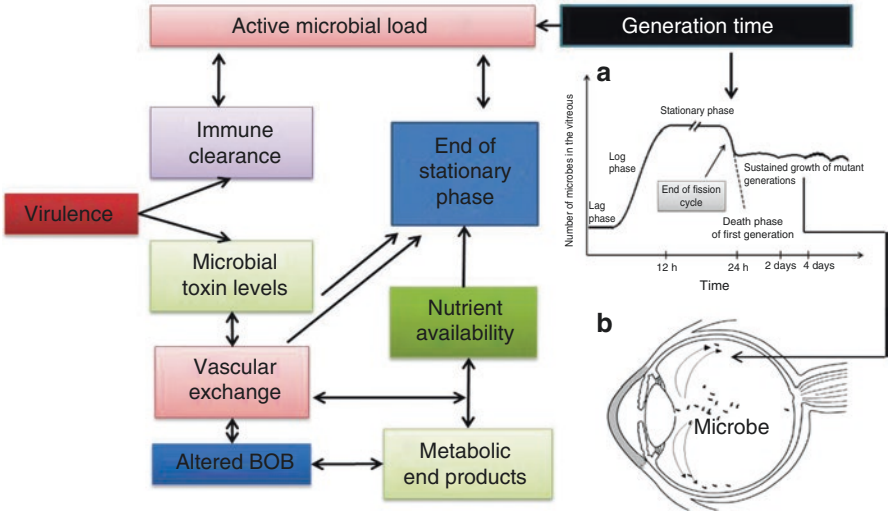

Fig. 23.1 Schematic representation showing the factors involved in the growth of microbes in the vitreous. *Insert* (**a**) shows the generation time and sustenance of microbial growth due to the availability of continuous supply of nutrients and their movement. *Insert* (**b**) toward the outer tunic and other tissues along with time. This hypothesis is supported based on the observations of Callegan et al. [12] using *B. cereus*, *S. aureus*, and *E. faecalis*

of this data into clinical endophthalmitis is limited only to a higher initial load of gram-positive bacteria inoculated into the eye (~100 CFU), its extrapolation could affect the event cascade on time scale for the majority of postoperative endophthalmitis. Along with the rapid multiplication of metabolically active bacteria, the vitreous liquefaction facilitates movement of microbes toward the outer tunic and other ocular tissues.

Microbial Toxins and Barrier Function

The metabolic end products and microbial virulent factors initiate inflammatory process in the cellular components of the eye leading to hypotony [12, 13]. The retinal tissue damage is irreversible and results in vision loss. Callegan's experiments further showed the rapid deterioration of retinal responses (electroretinogram, ERG) along with the exponential growth of bacteria in the vitreous humor within 12 h in *B. cereus*-infected eyes. *Pseudomonas* is reported to have a longer doubling time of ~3.5 h [14]. Studies using experimentally injected endotoxin of *E. coli* showed that the vitreous loaded with *E. coli* endotoxins cleared over 2 weeks [15]. This implies that the inflammatory damage caused by the endotoxins can persist in the eye for prolonged period, even after the microbial kill. Novosad et al. [16] reported elevated levels of cytokine and chemokine along with the involvement of toll-like receptors (TLR2) in infection of *B. cereus* endophthalmitis; TLR is integral to recognizing the invading organisms causing endophthalmitis. We do not know much about the initiation and extent of alteration of barrier function in terms of transporter susceptibility or paracellular transport of therapeutic agents in the entire cascade of events in endophthalmitis.

Pharmacodynamics of Antimicrobial Agents

Basically there are three models. The antimicrobial agents such as penicillin follow pharmacodynamic model of $T >$ MIC (time > minimum inhibitory concentration), where the concentration-dependent antimicrobial activity occurs over a narrow range of drug concentrations and the extent of antimicrobial activity is a function of the duration of effective exposure. Agents altering protein synthesis such as streptomycin follow C_{max}/MIC (maximum concentration/minimum inhibitory concentration) model, which shows concentration-dependent bactericidal effect over the range of drug concentration. Agents like vancomycin follow AUC/MIC (area under curve/minimum inhibitory concentration) model.

Apart from their direct action, postantibiotic effect is an additional parameter for an antimicrobial agent in maintaining its activity. Postantibiotic effect is the time period beginning after the organism is exposed to an antimicrobial agent until the survivors begin to multiply to a significant degree. A significant postantibiotic effect

is reported with agents inhibiting protein or nucleic acid synthesis such as macrolides, quinolones, tetracyclines, etc. [1]. Postantibiotic effect has been best correlated with the aforesaid PK/PD models of the known classes of antimicrobials [17].

In the Endophthalmitis Vitrectomy Study, a prospective study of post-cataract acute endophthalmitis, 94.2% of isolates were gram-positive pathogens [18]. Most of the antimicrobials approved for human use are for systemic use and are seldom studied for infections in the eye that is well protected by blood-ocular barriers. Systematic studies on various degrees of inflammation affecting the barrier function that in turn alters the pharmacokinetics of antimicrobial agents with differential susceptibility for transporters are not yet explored. The type of antimicrobial agent used and its frequency of dosing would determine the duration or the extent of its exposure leading to effective microbial control. Therefore, applying rational approaches with modified PK/PD assumptions is required to predict the intraocular penetration of antimicrobials in endophthalmitis of bacterial and fungal origins. Considering the complications and restrictions associated with the sampling techniques of ocular fluids, animal studies are often extrapolated to human use. Despite these studies, lack of appropriate data of plasma and corresponding intraocular level (anterior chamber fluid and/or vitreous) for an antimicrobial agent in normal and inflammatory conditions is a hurdle while applying PK/PD assumptions in endophthalmitis (Fig. 23.2).

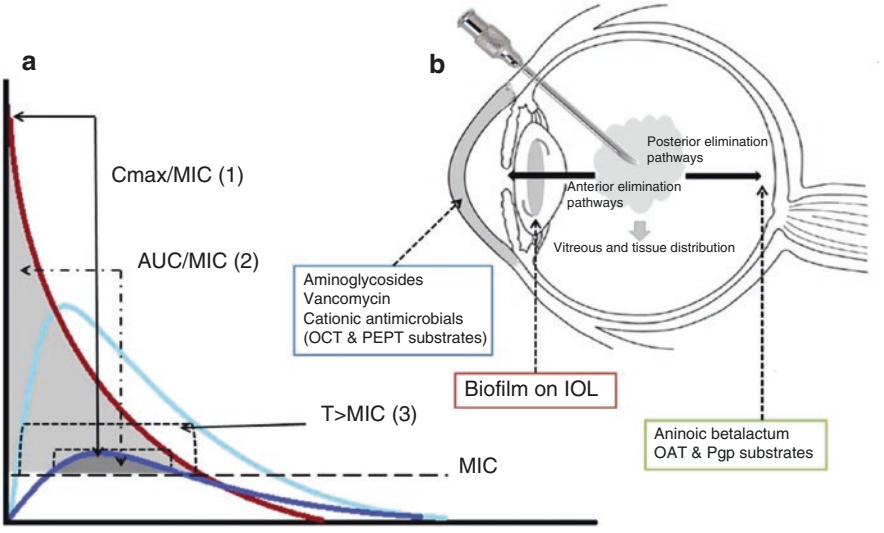

Fig. 23.2 (**a**) Graph showing the vitreous levels of an antimicrobial agent after oral administration along with its corresponding plasma levels as compared to direct intravitreal dosing. Typically aminoglycosides are capable of altering the microbial protein synthesis following Cmax/MIC, penicillin following $T >$ MIC, and vancomycin following AUC/MIC indicating the importance of selecting suitable antimicrobial agent for ocular therapy. (**b**) Showing the elimination pathways of intravitreally injected antimicrobials. Note: biofilm-forming bacteria on intraocular lenses are highly resistant to drug penetration

Factors Influencing the Antimicrobial Disposition in the Eye

Factors influencing ocular disposition of antimicrobial agents are conventionally discussed by the route of elimination, ionic nature, solubility coefficient of the drug, status of ocular inflammation, surgical status of the eye, molecular weight, vitreous liquefaction, solution density, and frequency of intravitreal administration [6, 19]. Increasing knowledge of the barriers of the eye has shown new inputs regarding the fate of ocular drug concentration based on their transporter susceptibility [2, 20–22]. Most of the antimicrobials are substrates of anionic, cationic, P-gp (P-glycoprotein), or PEPT (peptide) transporters as per their charge and molecular structure or characteristics [3]. This property determines their effective concentration in the ocular tissues after direct or systemic administrations.

The ocular kinetics of intravitreal gentamicin, eliminated by the anterior pathway, has been explained by Barza et al. in 1983 [23], and recently Nirmal et al. [22] described the elimination of intravitreally injected positively charged compounds based on the functional studies on the position of organic cation transporters (OCT) in rabbits. OCTs are present in ocular tissues in the intake position from the blood and the vitreous; their elimination is achieved through slow anterior pathway. Unlike substrates of P-gp eliminated through retinal pump mechanisms [24], intraocularly injected positively charged compounds follow relatively slow anterior elimination pathway. Therefore, positively charged compounds like ceftazidime, cefepime, and daptomycin (Fig. 23.3) are best suited for intraocular administration as they are unlikely eliminated through the retina, which is very rapid considering the surface area and orientation of transporters. Studies with the help of gamma camera have shown the retinal elimination of radiolabeled ofloxacin (P-gp substrate) via the retina by posterior drug efflux pathway [21]. This study has also shown that ofloxacin's vitreous elimination could be delayed by blocking the P-gp using verapamil.

Blood-Ocular Barrier in Ocular Pharmacokinetics

In the blood-eye interface, we consider two important barriers involved in the regulation of the exchange of endogenous compounds. The ciliary body and iris contribute toward the blood-aqueous barrier where influx of compounds from the blood into the eye predominates. The blood-retinal barrier regulates the major control over the inward and outward movement of compounds from the retina/vitreous [2]. Blood-retinal barrier is further divided into two types, the inner blood-retinal barrier (iBRB) and the outer blood-retinal barrier (oBRB). The continuous endothelial cell linings of the blood vessels of the neural retina form the iBRB; it rests on the basal lamina that is covered by processes of Muller glial cells and astrocytes [2]. Outer blood-retinal barrier is constituted by retinal pigment epithelium and choroid. These are tightly regulated structures; transport of nutrients plays a physiological role

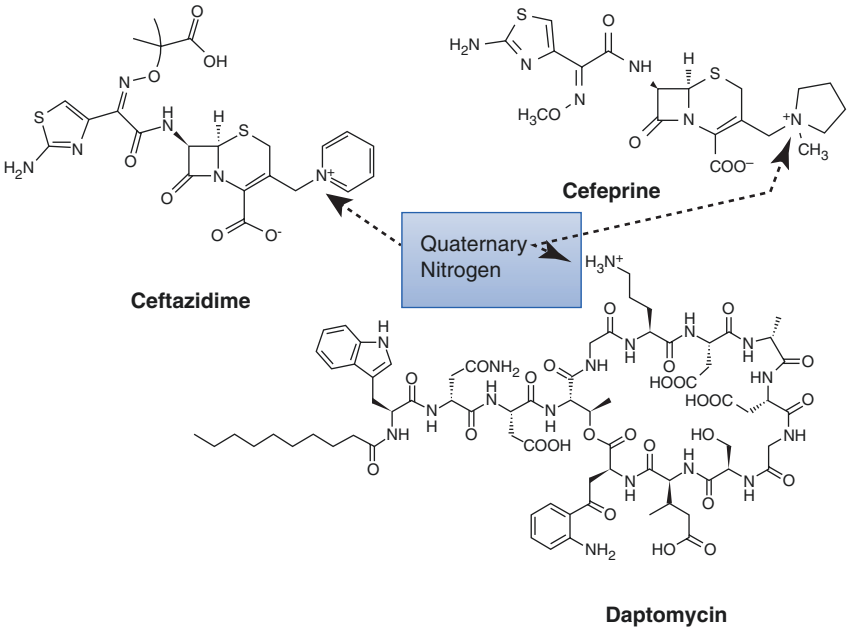

Fig. 23.3 Cationic antimicrobial agents that are found to have longer residence time in vitreous due to their substrate specificity for organic cation transporters (OCT) favoring anterior elimination pathway in the eye

under normal conditions, helping in retinal homeostasis through specific transporter mechanisms (Fig. 23.4).

Blood-aqueous and both retinal barriers of the retina (iBRB and oBRB) express transporters of physiological relevance that are involved in the transport of xenobiotics. The transporters relevant to ocular pharmacokinetics of drugs belong to variety of drug transporters in the ATP-binding cassette (ABC) and solute carrier (SLC) families. Among them P-gp, breast cancer resistance protein (BCRP), multidrug resistance-associated proteins (MRPs), organic anion transporters (OATs), organic anion transporting polypeptides (OATPs), bile acid transporters (ASBT and NTCP), OCTNs and MATE, and peptide transporters (PEPTs) have a potential role in ocular kinetics of drugs injected systemically or intraocularly [2, 20, 25]. Many systematic studies have shown the functional importance of these transporters in the influx and efflux of xenobiotics in blood-ocular barriers. OCT is functionally active in blood-ocular barriers and is involved in the transport of its substrate from the blood to vitreous humor and also in the uptake position in the cornea [26, 27]. P-glycoprotein transporters are involved in the efflux of intravitreally injected substrates, and they also block their systemically administered substrates from reaching adequate concentration inside the eye [28, 29]. Nutrient transporters like peptide transporters (PEPTs) are targeted for the enhanced uptake of peptide-based prodrug across blood-ocular barrier [30].

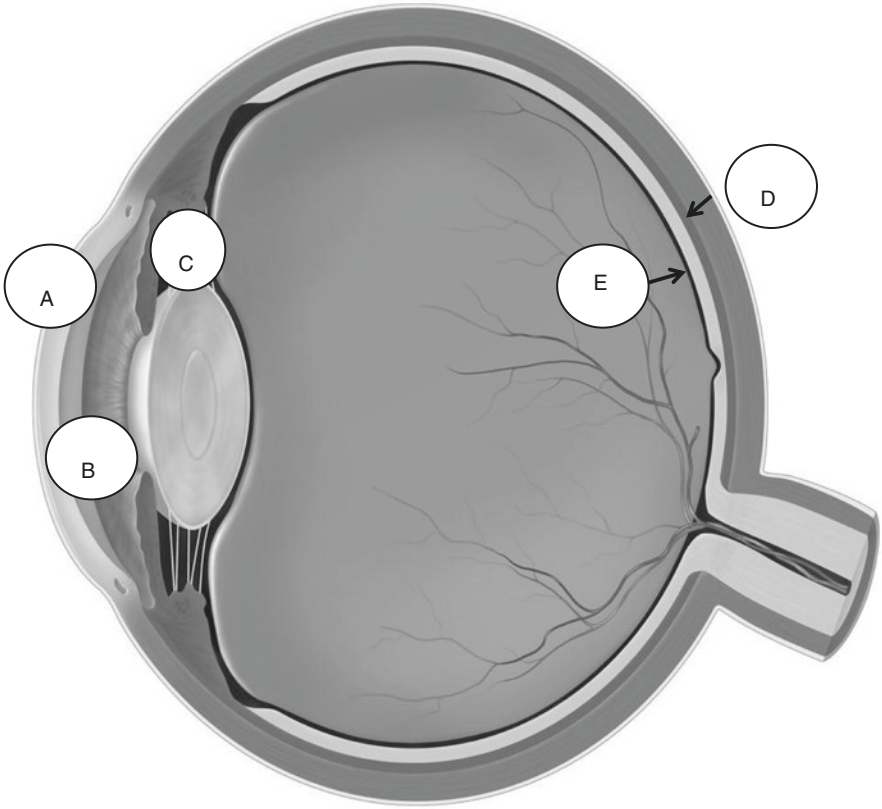

Fig. 23.4 Routes of exit for various intravitreal antibiotics. (*a*) Epithelial barrier, (*b*) aqueous-vitreous barrier, (*c*) blood-aqueous barrier, (*d*) outer retinal barrier, (*e*) inner retinal barrier (Adapted from Cunha Vaz JG, et al. Doc Ophthalmol 1997; 93:149–57)

Presence and function of organic anion transporters in the retinal elimination are known from the studies with intravitreal carbenicillin (OAT substrate) whose vitreous half-life was prolonged when treated with OAT inhibitor probenecid [23]. The presence of equilibrative nucleoside transporter (ENT) has been found in the retina [31] though their role in the ocular pharmacokinetics of drugs is not known. Although the presence of other transporters in the retina has been shown, their functional importance and alteration in various ocular pathological conditions remain unproven. As of now, except positively charged substrates like gentamicin, most of other compounds are reported to follow posterior elimination pathway through the retina. Therefore, the net result of inflammation induced in endophthalmitis on the expression and function of transporters in blood-retinal barrier is a matter of interest to understand the degree of antimicrobial drug influx after systemic administration or its elimination after intravitreal injection.

Effect of Endophthalmitis on Kinetics of Drugs

A meta-analysis on prophylactic use of antibiotics for prevention of endophthalmitis did not show a valid rationale; rather, a strict maintenance of aseptic conditions for ocular surgical procedure remains the gold standard infection prevention [4]. Ocular disposition of antimicrobials after intravitreal injection in normal and inflamed eyes has been extensively investigated in several animal and human studies [19, 32]. But, the rationale for the dose and frequency of repeat injections based on the pharmacodynamic model and toxicity is not available.

Effect of Inflammation on Ocular Penetration of Antimicrobials After Systemic Administration

There are very few reports that have investigated vitreous concentrations of antimicrobial agents in inflamed and normal eyes following systemic therapy. They do not help us understand the impact of inflammation-induced alteration of blood-ocular barriers. Rajpat et al. [33] have studied intraocular penetration of gatifloxacin after systemic therapy; they showed differential drug penetration into vitreous after oral administration of 400 mg in the patients undergoing vitrectomy in inflamed and non-inflamed circumstances. In the inflamed eye group, vitreous to plasma ratios at 2, 4, and 6 h after oral administration were 0.14, 0.27, and 0.28 in inflamed eyes and were 0.07, 0.21, and 0.26 in control (uninflamed) eyes, respectively. At a dose of 800 mg of gatifloxacin, this study documented an increase of 12.6% of drug concentration in an inflamed eye. Ferencz et al. [34] studied ocular penetration of vancomycin in patients undergoing vitrectomy for endophthalmitis after 1 gm intravenous injection. This study showed that vancomycin levels in vitreous increase with time to 2.04 ± 1.2 μg/ml in 4–5 h after the injection. The vitreous to serum ratio at 4–5 h after the intravenous injection was 0.16 in the infected eyes, not adequate enough for the expected antimicrobial activity [34]. Thus, one could conclude that infection-induced inflammation alters the barrier functions, though it cannot be relied upon as a dependable parameter.

Effect of Inflammation on the Clearance of Antimicrobials After Intravitreal Administration

Intravitreal injected antibiotic clearance in inflamed and uninflamed eyes has been studied by Meredith et al. [32] for the amikacin clearance via anterior route and by Ficker et al. [35] for cefazolin clearance via the posterior route. Table 23.1 lists the vitreous pharmacokinetics of intravitreally injected antibiotics in rabbits adopted from Meredith et al. [32], Ficker et al. [35], and Khamdang et al. [36] that has

Table 23.1 Showing the impact inflammation and clearance pathway on the kinetics of intravitreally injected antibiotics in rabbits (Data adopted from Ficker et al., Khamdang et al., and Meredith et al. [32, 35, 36])

Drug and its pathway	Status of the barrier	Intravitreal dose (mg)	Phakic			Aphakic			Aphakic + vitrectomy		
			24 h (μg/ml)	48 h (μg/ml)	T1/2 (h)	24 h (μg/ml)	48 h (μg/ml)	T/12 (h)	24 (μg/ml)	48 (μg/ml)	T1/2 (h)
Amikacin (anterior route)	Normal	0.4	100.9	55.6	25.5	25.3	15.3	14.3	15.5	3.0	7.9
	Inflamed	0.4	97.6	31.4	15.5	7.6	1.5	7.4	7.2	1.4	7.7
Cefazolin (posterior route)	Normal	2.25	147	8.97	6.5	183.3	17.7	8.3	25.7	3.7	6.0
	Inflamed	2.25	340	57.4	10.4	242.5	31.9	9.0	33.4	5.6	6.7

documented the effect of inflammation on the elimination pathways. It is apparent from Table 23.1 that inflammation and aphakia impact the drug elimination from the vitreous cavity. In a rabbit eye, inflammation and aphakia affect differently for the posterior route eliminated drug (e.g., cefazolin) and anterior route eliminated drug (e.g., amikacin, gentamicin). The vitreous concentration of cefazolin is higher and amikacin is lower in inflamed and aphakic eyes compared to normal phakic eyes. Keeping these facts in mind, antibiotic administration schedule must be optimized for maximal effect.

Intravitreal administration of antimicrobial agents based on their transporter susceptibility could be one of the rationale approaches in the treatment of endophthalmitis. As amikacin is expected to follow C_{max}/MIC > 8 for better clinical outcome [37], extrapolating this to the experimental data from the study of Meredith et al. [32] in the inflamed eye, the levels of amikacin would be able to exert antimicrobial efficacy approximately up to 24 h considering the MIC 90 of *Pseudomonas* for amikacin as 8 μg. Amikacin would be a good choice for 48 h for gram-negative organisms with lower MIC value. The knowledge about the transporter susceptibility of an antimicrobial compound along with its expected PK/PD model is essential for deciding its frequency and dose for intravitreal administration during endophthalmitis.

Rationale of Using Vancomycin with Ceftazidime or Amikacin Combination

The key objective of intravitreal antibiotic therapy of endophthalmitis is rapid sterilization of the vitreous cavity. Therefore, selection of antimicrobial agent for endophthalmitis should not only be based on its spectrum but also on their property of favorable PK/PD profile in vitreous in addition to less intraocular toxicity. Due to the uncertainty over intravenous antibiotic therapy, direct intravitreal antibiotic injection was the first point of management in the Endophthalmitis Vitrectomy Study (EVS) [18].

The well-accepted combination of intravitreal vancomycin and ceftazidime or amikacin as the first line of treatment in acute bacterial endophthalmitis is based on the outcome of various experimental/clinical studies [38]. We have explained the rationale of such a combination using their ocular pharmacokinetics in inflammatory conditions, their transporter susceptibility leading to predominating route of elimination along with their accepted antimicrobial PK/PD correlation.

Vancomycin

Vancomycin is a glycopeptide antibiotic that is effective against gram-positive bacteria including the MRSA (methicillin-resistant *Staphylococcus aureus*). Direct evidences lacking though, being a glycopeptide, vancomycin's susceptibility for peptide

transporters that are generally known to be in the uptake positions of cells could best explain the longer vitreous bioavailability duration after intravitreal administration. Peptide transporters belong to the PTR family; they have the ability to transport peptidomimetics and other substrates with therapeutic activities or peptide-derived pharmacological agents across the biological interface [30, 39]. After the intravitreal administration of 1 mg of vancomycin in the MRSA model of endophthalmitis in rabbits, vitreous concentrations of 266 ± 29 μg/ml, 85 ± 44 μg/ml, 28 ± 17 μg/ml, and 3 ± 1.4 μg/ml were detected on days 1, 2, 4, and 7, respectively [40]. Ocular pharmacokinetic studies in humans revealed a vitreous level of 58–137 μg/ml 2 days after the intravitreal injection of 1 mg of vancomycin in *Streptococcus viridans* and *Enterococcus faecalis* endophthalmitis [34].

Using the neutropenic mouse thigh infection model, vancomycin is reported to follow AUC/MIC for its antimicrobial efficacy. A ratio of AUC/MIC ≥ 400 is probably associated with the better clinical outcome for bacteriological response in patients with respiratory tract infections with *Staphylococcus aureus* [41]. While applying it on the experimental endophthalmitis study of Lefèvre et al. [40] in rabbits, $AUC_{0–24h}$/MIC ratio of 29,359 and $AUC_{1–7day}$/MIC ratio of 22,104 for MRSA could be derived if we consider the MIC of MRSA as 0.5 μg/ml. The values are multiple folds higher than the required levels (AUC/MIC ≥ 400 μg), and thus, it justifies the rationale of using intravitreal vancomycin in endophthalmitis. What holds true for the glycopeptides like vancomycin also holds true for the lipopeptide like daptomycin for endophthalmitis treatment.

Ceftazidime

Ceftazidime is a positively charged cephalosporin that is effective against gram-negative bacteria including *Pseudomonas*. Unlike other antimicrobials, cephalosporins like cephaloridine, cefoselis, cefepime, cefluprenam, and ceftazidime have quaternary nitrogen which carry positive charge and are reported to be the substrates of OCTN2 [42]. Using positively charged substrate of tetraethylammonium, Nirmal et al. [26] reported that intravitreally injected OCT substrates may follow an anterior elimination route and prolonged presence in vitreous humor. Gene expression studies revealed the presence of OCT1, OCTN1, and OCTN2 in various ocular tissues, and further studies suggested the presence of functionally active OCT in blood-ocular barriers that are involved in the transport of their substrates from the blood to vitreous humor [27]. Two hours after intravenously injecting 50 mg/kg of ceftazidime in rabbits, Aquilar et al. [43] reported a vitreous concentration of 35.4 μg/ml in the inflamed eyes.

Following intravitreal administration of ceftazidime at the dose of 2.25 mg, a vitreous half-life of 13.8 h and 10.1 h has been reported in phakic control and inflamed eyes (induced by heat-killed *S. epidermidis*), respectively [44]. At the end of 48 h, the ceftazidime levels were 139 ± 56 μg/ml and 56.5 ± 6.1 μg/ml in control and inflamed eyes, respectively. Interestingly, aphakic control and inflamed eye vitreous half-life was 11.8 h and 8.7 h with the vitreous levels of 48.5 ± 39 μg/ml

and 19.1 ± 10 μg/ml, respectively. PK/PD analysis of ceftazidime showed that improved clinical outcomes are associated with a free drug concentration exceeding the MIC for > 45–70% of the dosing interval which follows % T > MIC model [45]. Extrapolating the %T > MIC model of ceftazidime for its intravitreal use at the dose of 2.25 mg, existing data shows its presence up to 48 h in phakic or aphakic inflamed eyes up to the extent of 20 μg/ml, which is above most of the gram-negative bacteria including nonresistant species of *P. aeruginosa* having the MIC of 8 μg/ml [46].

Imipenem

Carbapenems are the newer class of β-lactam antibiotics having β-lactam ring with chemical modifications that makes them different from penicillins. Imipenem acts like penicillin but is resistant to the hydrolysis by most of the β-lactamases. Imipenem acts against most strains of *Pseudomonas* and β-lactamase producing penicillin-resistant strains of gram-positive bacteria. It is a substrate of organic anion transporters (OAT-3) like other anionic penicillins [47]. Clinical isolates of *Pseudomonas* are susceptible to imipenem [48]. Das et al. [49] reported that both meropenem and ertapenem penetrated the vitreous cavity of non-inflamed eyes with single intravenous dose but it was insufficient to attain therapeutic level. Intravitreal imipenem could be a choice for *Pseudomonas* infections; however, no ocular pharmacokinetic study is currently available to justify its use. Extrapolating its susceptibility to OAT and pharmacodynamic model of *T*/MIC, imipenem may not be suitable for intravitreal injection, as they may not have vitreous presence longer than the time required to be above the minimum inhibitory concentration for its optimum PK/PD correlation.

Future Prospects of Ocular Antimicrobial Therapy for Endophthalmitis

It is now understood that organic cation/carnitine transporters and peptide transporters are located in the intake position from the blood to vitreous and elimination is primarily through anterior route. Therefore, drugs having positive charge are best candidate for systemic to ocular transfer, and once it is injected intravitreally, its elimination is prolonged due to slow anterior elimination. Drugs that are substrates of organic anion transporters (OAT) and P-gp transporter substrates are present in efflux position from the eye in the retinal pathway; therefore, reaching adequate concentration either by systemic or increased vitreous levels and bioavailability time after intravitreal route would be inadequate especially to follow %*T*/MIC, AUC/MIC models of antimicrobial activities.

Recent studies support alternative substitutes for vancomycin like daptomycin (lipopeptide). Daptomycin has quaternary nitrogen in its structure and shows a longer vitreous residence time with a low MIC for MRSA after 1 mg intravitreal injection. Due to low MIC and higher vitreous bioavailability time, daptomycin showed ten times higher $AUC_{(1–7day)}$/MIC than vancomycin for MRSA [40]. Similarly, cefepime, a subtract of OCTN, is another member of cephalosporin having positive charge [42]; it is known to have excellent activity against gram-negative bacilli including *Pseudomonas aeruginosa*. It is more potent than ceftazidime against gram-positive cocci [50]. In an experimental *P. aeruginosa* endophthalmitis, intravitreal cefepime was found a suitable alternative to ceftazidime in treatment of *P. aeruginosa* endophthalmitis [51]. All these findings are consistent with the positively charged compounds in physiological pH, and substrates for ocular OCTs share better pharmacokinetic profile after intravitreal administration.

Conclusion

In the eye, adequate concentration of antibiotic reaching through systemic circulation or injected directly into the vitreous to meet the concentration or time-dependent MIC criteria (PK/PD) of invading organism is a deciding factor for the clinical outcome. Early identification and appropriate antimicrobial strategy would be effective in controlling the rapidly multiplying organism to minimize the damage to the retina. Along with the global increase in antimicrobial drug resistance, rationalizing the decision for the use of appropriate antimicrobial agent linking their elimination pathway with antimicrobial PK/PD is the new task. Development of newer positively charged cephalosporins creates a possibility of choosing newer compounds with better MIC values than the old ones to cover gram-negative infections. Similarly, development of newer glycopeptides or lipopeptides like daptomycin is giving new hope for gram-positive and resistant organisms like MRSA. However, inappropriate use of antibiotic and in suboptimal concentrations in the initial generation time of bacteria would end up with more resistant secondary generations that will be difficult to treat.

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Part IV
Science of Endophthalmitis Treatment: Microbiology

Chapter 24
Microbiology: Collection of Ocular Specimens, Processing and Interpretation of Results

Savitri Sharma

Endophthalmitis management calls for a quick diagnosis and prompt therapy. Despite the preferred practice of intravitreal injection of broad-spectrum antibiotics against gram-positive and gram-negative bacteria as soon as the clinical diagnosis of infectious endophthalmitis is made, it is important to establish the etiological diagnosis. The following reasons may be put forward to support the use of microbiological investigations in the management of infectious endophthalmitis:

1. Adapt the management strategies to the known virulence of the organism.
2. Reassess the epidemiology of microorganisms associated with different types of endophthalmitis in particular geographic areas.
3. Establish the trend of antimicrobial susceptibility of the prevalent organisms.
4. Aid in relevant research towards advent of better diagnostic techniques and better treatment strategies.

Similar to microbiological investigation of any other infective disease, appropriate processing of the right clinical sample is of paramount importance in the diagnosis of infectious endophthalmitis. Also important is the knowledge of expected organisms and application of new available tests on the block.

Collection, Processing and Interpretation

Types of Clinical Sample

The best sample for the investigation of infectious endophthalmitis is the intraocular fluid. Both aqueous and vitreous fluids are useful. However, nearly 50% of aqueous cultures may be negative in cases of postoperative endophthalmitis with positive

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vitreous cultures, [1] and in certain situations, it may be the other way round [2]. Any intraocular inflammation that is unresponsive to intensive topical corticosteroids may warrant collection and culture of intraocular fluids. Some of the other guidelines would include hypopyon in absence of a known predisposing factor, beaded opacities or white plaques in the anterior chamber and/or vitreous not responding to topical corticosteroids, opacified conjunctival filtering bleb, etc. The presence of a corneoscleral defect following trauma or presence of inflammation, even if mild, following recent suture removal should raise suspicion of endophthalmitis and warrants immediate microbiological investigation to rule out intraocular infection [3].

In chronic postoperative endophthalmitis, apart from intraocular fluids, intraocular plaques with or without intraocular lens (IOL) should be cultured. Filtering bleb-associated endophthalmitis may require collection of samples such as bleb contents apart from aqueous and vitreous.

Vitreous provides the most dependable results always [4]. Different microorganisms may be cultured from intraocular fluid and conjunctival swabs; therefore, conjunctival cultures could be misleading in patients with infectious endophthalmitis [5, 6]. It is difficult to decide which specimen to culture in endogenous endophthalmitis. While value of vitreous culture and smear is unquestioned, the utility of blood culture, urine culture, cerebrospinal fluid culture and culture from other body sites is controversial [3]. The decision to include samples other than from the eye will depend on the site of original infection and specific events that may clinically connect with the episode of endogenous endophthalmitis. Consultation with the treating physician may help to decide.

In posttraumatic endophthalmitis, culture of retained intraocular foreign body and debrided or excised tissue should be cultured along with intraocular fluids. However, caution must be exercised in the interpretation of the culture results of extraneous materials as they may represent contamination without resultant infection [7].

Collection and Transport Procedures

A 1 mL tuberculin syringe with 30-gauge needle of 5/8-in. length can be used for aspiration of 0.1–0.2 mL aqueous fluid through the limbus. Vitreous biopsy using a vitreous cutter is considered a better sample than vitreous aspirate because of better culture positivity and less vitreoretinal traction [8]. While 0.1–0.2 mL vitreous can be aspirated through limbus using 1-in. 25–27-gauge needle on tuberculin syringe, vitreous biopsy requires one-, two- or three-port vitrectomy, and one could obtain 0.5–1.0 mL of vitreous. A safer method using a butterfly needle is described where the length of the tubing works as the reservoir for collection of undiluted vitreous [9]. An undiluted vitreous is the ideal sample. Aqueous and vitreous aspiration and one-port vitrectomy have been used as office procedures; however, in certain environmentally compromised setups, it is safer to conduct these procedures in the operating room.

Intraocular fluids collected in syringe should be sent to the laboratory wrapped in sterile plastic cover/envelope. The needle can be capped prior to wrapping the syringe. There is a suggestion that the intraocular fluid collected in a syringe should be transported with a bent needle or the needle struck to a sterile rubber cork [10]; however, there is no experimental evidence of benefits of this transport method. In case of delay in sending to the microbiology laboratory, the syringe should be held for not more than overnight in the refrigerator at 2–8 °C and should not be frozen. Anaerobic organisms are sensitive to oxygen and refrigeration; these organisms could be lost unless processed immediately. Secure box with ice packs may be used for distant transport. Alternatively, the sample could be inoculated on culture media in the operating room leaving a small quantity in the syringe for making smears on arrival in the laboratory. Some time ago, a recommendation was made that along with vitreous biopsy one could submit the cassette fluid for culture, and the study showed higher percentage of culture positivity rate at 76% compared to vitreous biopsy specimen positivity at 43% [8]. These results were corroborated in another study by Sharma et al. [11]. Explanted IOL, intraocular foreign body, intraocular plaques, capsular material and filtration valves are best submitted to the laboratory by placing directly on a sheep blood agar plate. Intraocular fluid for molecular diagnosis can be stored at -20 °C in microcentrifuge tubes until use.

Processing of the Clinical Material in Microbiology Laboratory

Immediate processing of the samples is highly critical. Essentially, the volume of the sample decides the number of culture media to be included. The objective is to include procedures that would allow quick diagnosis by visualization of bacteria and/or fungi in direct microscopy and also to allow growth of both bacteria and fungi in the culture. Drops of samples received in syringe are aseptically (preferably inside laminar flow biosafety hood) delivered on the surface of solid and liquid culture media and in the centre of glass slides. It is not necessary to spread the drops on the slides or plates unless the sample is purulent. Smears should neither be very thick nor thin. Sterile wire loops may be used for the purpose. A thick smear may detach from the slide while staining, and a thin smear will spread the organisms and cells too much making the microscopic examination difficult. The drops are allowed to air dry and fixed with absolute methanol prior to staining. For better cellular morphology, methanol fixation is preferred over heat fixation. Methanol fixation may not be required when a wet mount (e.g., calcofluor white stain) is contemplated. A few publications have mentioned the use of cytospin or centrifugal cytology bucket [10, 12] for preparation of smears from intraocular fluids; we have had no experience with this and have found smears made from drops of the fluids adequate for the purpose.

Direct Microscopy Methods

Currently an ideal point of care test for the microbiological diagnosis of endophthalmitis is unavailable. The only test that can provide diagnosis within an hour and with minimal requirements for space, instrumentation and reagents is the microscopic examination of the stained smears of intraocular fluids by Gram stain and Giemsa stain [13]. However, in general, smear examination is less sensitive and specific compared to vitreous culture [6, 11]. Consistency between smear and culture results varies between 50 and 67% [14, 15]. Examination of unstained wet mount of vitreous sample offers little advantage and has been replaced by calcofluor stain wet mount and forms a standard protocol in our laboratory in addition to Gram and Giemsa stain. This stain is very useful for detection of yeast and other fungal elements in direct microscopy of intraocular fluids. We also subject smears to Gomori methenamine silver (GMS) stain for visualization of fungal elements. A gram-stained smear can be restained with GMS stain for the purpose. Detailed account of methods of fixation and staining with variety of stains can be found elsewhere [15, 16].

Culture Methods for Bacteria and Fungi

Table 24.1 provides the list of direct microscopy methods and culture media that are recommended for processing of intraocular fluid for detection of bacteria and/or fungi.

Table 24.1 Type of stains for smears and media for culture of intraocular fluids for the laboratory diagnosis of infectious endophthalmitis

Type of sample	Expected organisms	Stains/media/incubation		
Aqueous fluid/vitreous fluid/vitreous biopsy	• Bacteria, fungi • Fungi	• Gram, Giemsa • Calcofluor white, Gomori methenamine silver		
	Bacteria (aerobic and anaerobic) and fungi	Sheep blood agar	Aerobic	37 °C
		Sheep blood agar	Anaerobic	37 °C
		Sheep blood chocolate agar	CO_2	37 °C
		Brain-heart infusion broth	Aerobic	37 °C
		Thioglycollate broth	Aerobic	37 °C
		Sabouraud dextrose agar[a]	Aerobic	27 °C
		Robertson's cooked meat broth	Aerobic	37 °C

[a]With antibiotics (gentamicin or chloramphenicol) but without cycloheximide. Potato dextrose agar may be used in addition to Sabouraud dextrose agar for better sporulation

The table also lists the incubation condition for each medium. It is advisable to incubate all media for at least 1 week and Sabouraud dextrose agar for at least 2 weeks. If the vitreous received is diluted by irrigating fluid such as in a vitrectomy cassette and is in excess of 2 mL, it is advisable to filter through membrane filter attached to a syringe and pieces of the filter paper could be inoculated in various media [8, 11]. A blood culture method was shown to increase the culture positivity by 29% [16, 17]. The authors found significantly more culture-positive results, especially gram-positive organisms, compared to membrane filter method and concluded that the blood culture bottle offered a technically easier method compared to membrane filter method for the culture of vitreous sample.

Interpretation of Smear Results

Across various studies, smear results are reported to be significantly less sensitive than the culture; however, being a rapid procedure, it is considered useful [6]. The presence of uveal pigments (brown, oval or round) in the smears is one of the difficulties faced by the microbiologists during microscopy, especially in Gram and Giemsa stain where the round pigments may resemble staphylococci in shape and size and the oval pigments may resemble corynebacteria (Fig. 24.1). Giemsa stain helps determine the type of inflammatory response.

A correlation of type and quantity of cells and culture results made earlier did not show any significant difference in the culture-positive and culture-negative samples as well as between samples from patients with bacterial or fungal endophthalmitis [11]. A mononuclear cellular response may be indicative of a viral infection, and an eosinophilic response may suggest parasitic infection [6]. In phacolytic endophthalmitis, one may find macrophages laden with lens matter in the vitreous. Bacteria that can be discerned well in Gram stain of vitreous fluid include gram-positive cocci in pairs, short chains or groups (Fig. 24.2 top left) suggestive of staphylococci

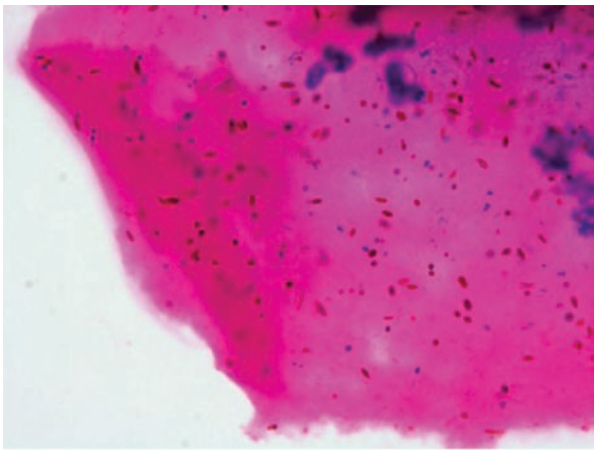

Fig. 24.1 Vitreous sample microscopy showing polymorphonuclear cells and gram-positive cocci along with round and oval brown uveal pigments (gram stain; total magnification 1000×)

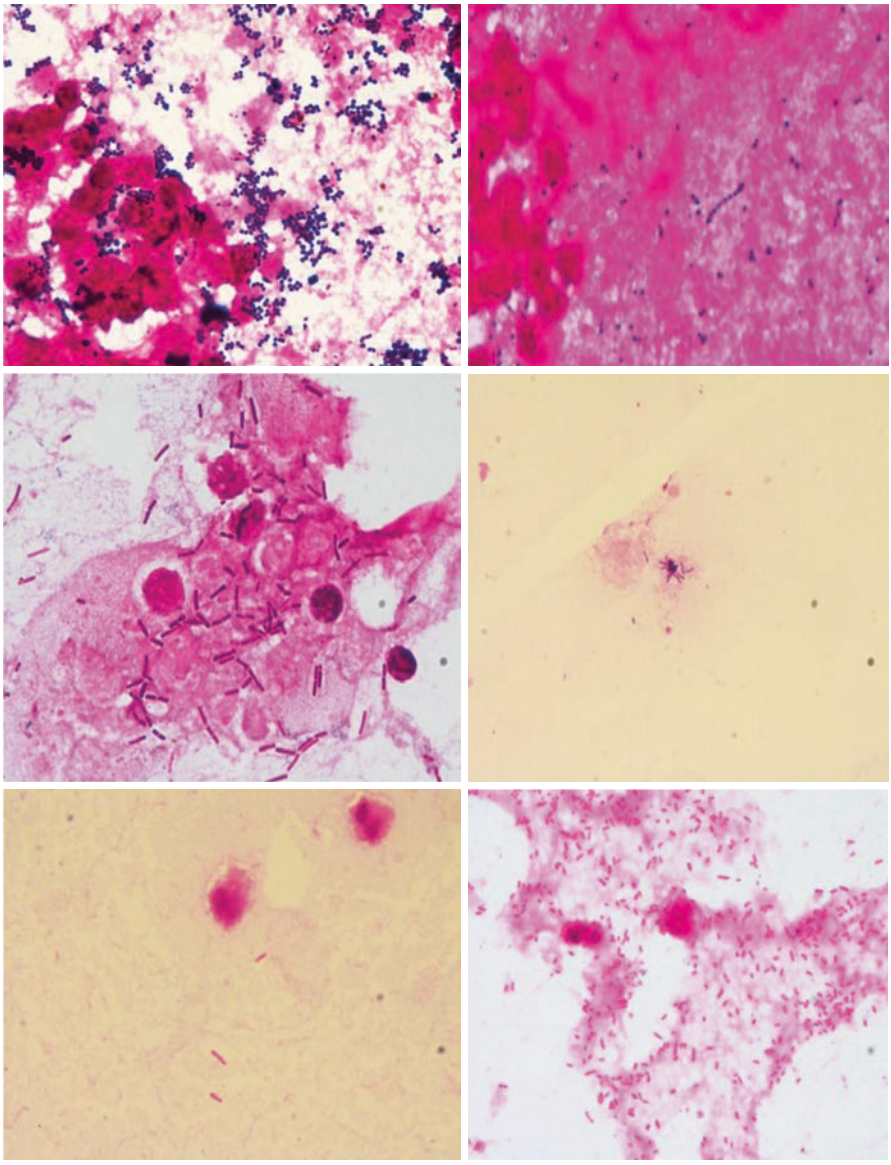

Fig. 24.2 Microscopy of vitreous sample. *Top left***,** polymorphonuclear cells with gram-positive cocci in pairs and groups suggestive of *Staphylococcus* species; *Top right***,** gram-positive cocci in pairs and short chains suggestive of *Streptococcus* species; *middle left***,** long, thick and beaded gram-positive bacilli in chains, suggestive of *Bacillus* species; *middle right***,** gram-positive bacilli occurring in Chinese letter pattern suggestive of *Corynebacterium* species; *bottom left*, gram-negative slender long bacilli suggestive of *Pseudomonas* species; *bottom right***,** stout gram-negative bacilli suggestive of *Enterobacteriaceae*

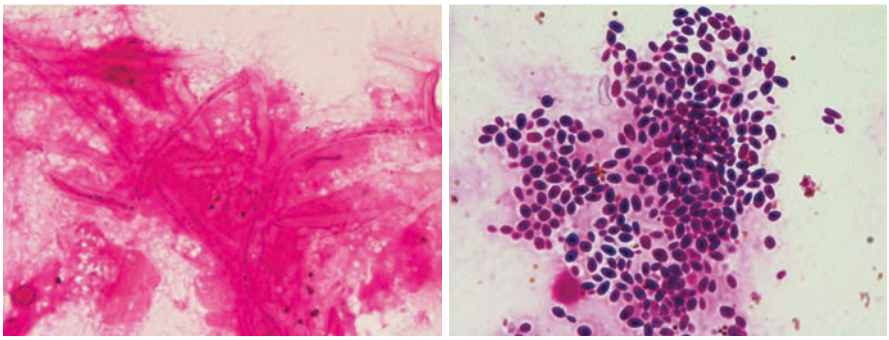

Fig. 24.3 Microscopy of vitreous sample. *Left*, hyaline, septate fungal filaments suggestive of mould (gram stain, 1000×) and *right*, budding yeast-like cells suggestive of *Candida* species

and in pairs and short chains with lanceolate shape and capsule suggestive of *Streptococcus pneumoniae* (Fig. 24.2 top right). Long and beaded gram-positive bacilli, often in chains, would suggest *Bacillus* group of bacteria (Fig. 24.2 middle left) and occurring in L- and V-shaped arrangements (Chinese letter pattern) would be *Corynebacterium* sp. (Fig. 24.2 middle right). *Pseudomonas* appears slender, often long, gram-negative bacilli (Fig. 24.2 bottom left), and stout gram-negative bacteria could be enterobacteria (Fig. 24.2 bottom right).

Many of these bacteria may be seen intracellular in polymorphonuclear cells and macrophages. Smears are always reported with morphological description and may at best be suggestive. They need confirmation by culture. However, knowledge of whether gram-positive or gram-negative bacteria is itself of immense value. Unlike bacteria, the type of fungus is difficult to guess based on morphology in smear.

Fungal filaments (Fig. 24.3 left) are reported as either hyaline or brown and septate or aseptate. A specific fungus yeast cells with budding could be suggestive of *Candida* sp. (Fig. 24.3 right). Detection of fungal elements in direct microscopy calls for a critical alert for managing the patient with intravitreal antifungal therapy.

Interpretation of Results of Culture and Antimicrobial Susceptibility Testing

It is important to establish the significance of the organism isolated in culture. It is helpful to follow the guideline suggested in many publications that includes a significant growth (Table 24.2).

Standard microbiological procedures, beyond the scope of this chapter, are followed to establish the genus and species of the bacterial or fungal isolates. Replacing conventional biochemical methods, the modern automated systems such as VITEK 2

Table 24.2 Significant microbiological growth

1. Confluent growth on the inoculum in any solid medium
2. Growth in more than one medium
3. Growth in one medium with presence of the same organism in direct microscopy
4. Occasionally, an isolate grown in one liquid medium may be considered significant, especially, if it is not a common external ocular flora[6]

compact system (next generation of API systems) and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToF MS) are being increasingly adopted for accurate identification of bacteria and fungi.

Kirby-Bauer disc diffusion assay using CLSI (Clinical and Laboratory Standards Institute) guidelines is widely used for testing susceptibility of clinical bacterial isolates to various antibiotics. VITEK 2 compact system also helps in determining antimicrobial susceptibility and provides minimum inhibitory concentration (MIC) of drugs, which is considered superior to disc diffusion assays in measuring *in vitro* drug susceptibility of bacterial isolates. It is common for many laboratories currently to use E test to determine MIC of drugs against bacteria and yeast [18, 19]. Certain drugs such as ceftazidime, vancomycin, piperacillin-tazobactam, colistin, imipenem, etc. require MIC testing for confirmation of resistance indicated on the basis of disc diffusion assays. Susceptibility of filamentous fungal isolates to antifungal drugs is not tested commonly. When required, CLSI-based micro-broth dilution method can be used.

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Chapter 25
Molecular Methods in the Diagnosis of Endophthalmitis

Savitri Sharma

The value of conventional smear and culture of intraocular fluids in the diagnosis of infectious endophthalmitis is obvious in the earlier chapter. However, negative results in the presence of clinical signs of infection pose a challenge to the treating ophthalmologist. In addition, it may take 2–4 days for fastidious organisms to grow in culture and longer for some of the fungi. Apart from fastidious organisms, the causes for culture-negative results in the presence of infection can be many such as small sample size, sequestration of bacteria or fungi in the capsule or intraocular lens or lens remnants, prior antibiotic therapy, or delay in processing of the sample. Advances in molecular microbiology have provided an opportunity to the clinical microbiologists to improve microbiological diagnosis in clinical samples. Techniques that were for long confined to research laboratories have made their way into clinical microbiology laboratories. These tests have enhanced the utility of laboratory diagnosis in the treatment of infectious endophthalmitis by complementing the conventional microbiological methods. Some of these methods include polymerase chain reaction (PCR) and real-time PCR.

Polymerase Chain Reaction (Box 1)

Polymerase chain reaction (PCR), a powerful molecular tool, has been successfully used in the detection of DNA of microorganisms in the intraocular fluids. This detection system does not require the presence of viable organisms and is suited for diagnosis of culture-negative cases where the antibiotic therapy has already been initiated. Primers are designed to either help detect a particular organism or a group of organisms. PCR is highly specific and sensitive at the same time, thus requiring validation in disease-free control subjects [1].

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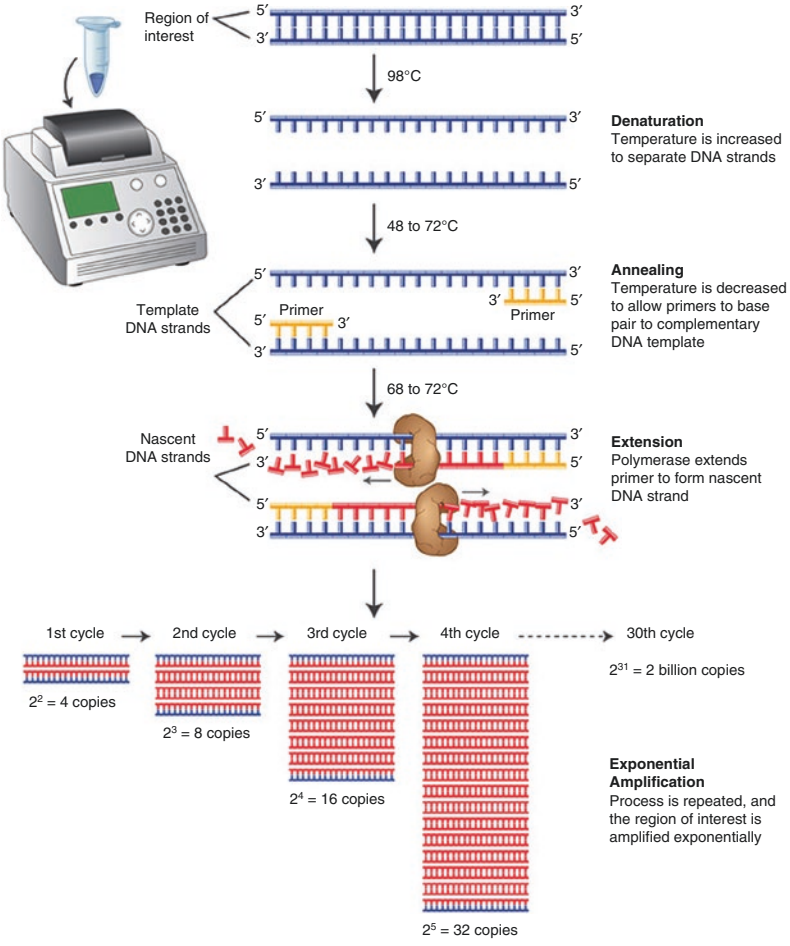
Panbacterial, universal, or eubacterial PCR using 16S rDNA gene primers has been extensively used for the diagnosis of bacterial endophthalmitis [2–4]. The detection limit by nested PCR has been determined to be one organism in one study [1]. False-positive result due to impure Taq DNA polymerase while using eubacterial primers in PCR has been a challenge to the investigators [1, 5]. Several investigators have suggested methods to overcome this problem [5, 6]. A multiplex PCR with gram-negative- and gram-positive-specific primers has been used with aqueous and vitreous samples [4]. The study has shown high concordance between PCR and culture results. Similar to eubacterial PCR, several studies have reported application of panfungal PCR in the diagnosis of infectious endophthalmitis. Primers based on 18S rDNA, ITS region, or 28S rDNA have been used [7–9]. These PCR tests are reported to be highly specific and sensitive to detection level of 1 fg of fungal DNA. Compared to culture ITS region-based PCR was reported to show increased detection of fungal endophthalmitis in 28.6% cases [9].



(Courtesy:https://www.neb.com/~/media/NebUs/Page%20Images/Ap plications/DNA%20Amplification%20and%20PCR/pcr.jpg)

Box 1 Polymerase chain reaction (PCR)
In cycle 1 two primers anneal to denatured DNA at opposite sides of the target region and are extended by DNA polymerase to give new strands of variable length. In cycle 2, the original strands and the new strands from cycle 1 are separated, yielding a total of four primer sites with which primers anneal. The primers that are hybridized to the new strands from cycle 1 are extended by polymerase as far as the end of the template, leading to a precise copy of the target region. In cycle 3, double-stranded DNA molecules are produced that are precisely identical to the target region. Further cycles lead to exponential doubling of the target region. The original DNA strands and the variably extended strands become negligible after the exponential increase of target fragments.

Post-PCR Species Determination

Following panbacterial and panfungal PCRs, a second step is required to identify the species of bacteria or fungus. A variety of methods including sequencing of the amplified DNA, hybridization with specific probes, or restriction fragment length polymorphism (RFLP) have been used, of which sequencing is most common [10]. Sequence of the amplified DNA is compared with similar sequences in databases using NCBI BLASTn 2.2.26 program of the National Center for Biotechnology Information (NCBI, GenBank database). Usually, a score of 97% and similarity of 98% allow the genus recognition, and a score of 99% or more may assign a species name. More reliable is the identification based on phylogenetic analysis, which shows the phylogenetic distance between the analyzed sequence and the sequences in the databases. Phylogenetic analysis allows comparison with type strains available in the databases.

In hybridization technique, the amplified DNA obtained from the sample is denatured and transferred on a membrane (dot blot assay) to which are added labeled (radioactive isotopes, fluorophores, haptens like biotin or digoxigenin or an enzyme) specific probes. The probes are usually a short strand of oligonucleotide specific for hybridization with complementary sequence of either a species of organism or a group of organisms such as gram-negative or gram-positive bacteria. Conversely, in DNA chip technology, complementary sequences to signature genes of specific organisms or groups of organisms are dotted on the chip. To this is added multiplex PCR-amplified biotin-labeled denatured DNA (of the sample) that would hybridize to complementary DNA on the chip. Enzyme-labeled streptavidin in the next step would reveal the specific gene by color development on addition of the substrate [11].

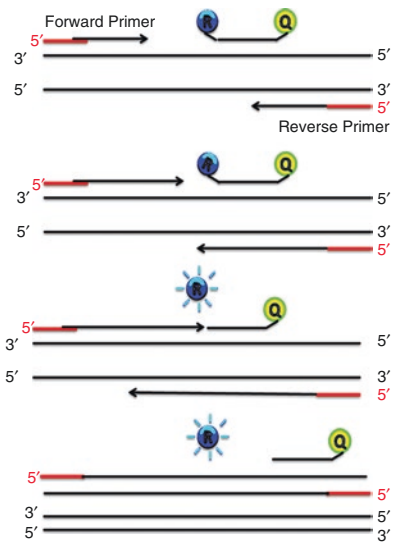
In PCR-RFLP, the bacterial and fungal genome can be identified by their genetic fingerprint produced by the use of restriction enzymes on the amplicons. The number of fragments is proportionate to the number of restriction sites in the genome and is specific for particular species [1].

When species identification has been attempted, most studies have used sequencing compared to RFLP and hybridization [10, 12]. Value of PCR in the diagnosis of endophthalmitis caused by anaerobes such as *Propionibacterium acnes* has been well established [8]. Causative role of rare fungal species like *Colletotrichum truncatum* in endophthalmitis has been confirmed by sequencing of internal spacer regions of ribosomal DNA [13].

Aforementioned methods mostly identify mono-microbial infection. An entirely different approach through cloning 16S rRNA gene and next-generation sequencing has shown a polymicrobial etiology of infectious endophthalmitis [14]. The authors identified several novel bacteria associated with endophthalmitis.

Real-Time PCR

Recent studies have reported application of real-time qualitative or quantitative PCR in the diagnosis of infectious endophthalmitis. Most diagnostic applications of real-time PCR are qualitative. Quantitative PCR, the qPCR, determines the amount of DNA in the sample and can be absolute or relative. Real-time PCR requires a special thermocycler that measures fluorescence, which is produced in proportion to the amplification of the DNA, cycle by cycle (Box 2).

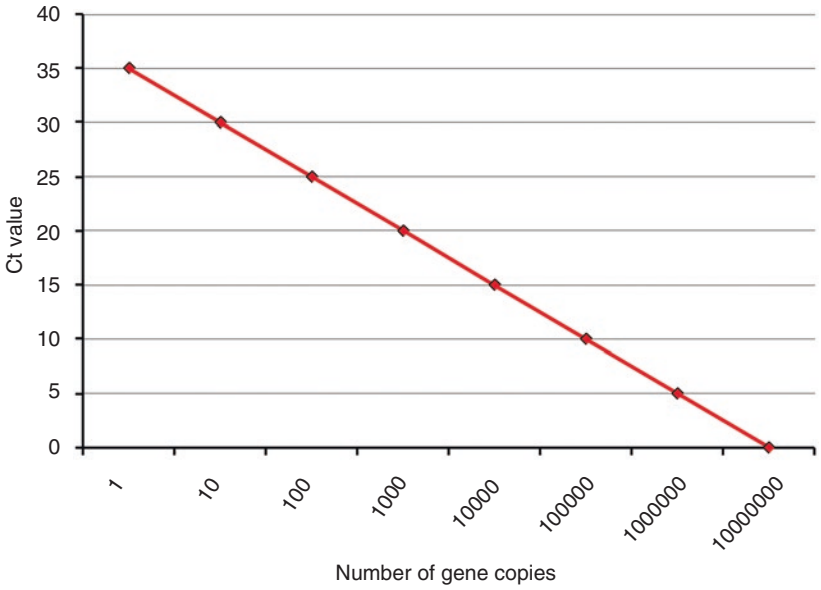


1. Polymerization: A reporter dye and quencher was attached to Taqman probe

2. When probe is intact, the reporter dye emission in quenched

3. Cleavage: During each extension cycle, the DNA polymerase cleaves reporter dye from the probe

4. Polymerization completed: Once separated from the quencher, the reporter dye emits its characteristic fluorescence



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Box 2 Real-time PCR

Top—The template is amplified by primers and the amplicon allows for annealing of sequence-specific, labeled probes. As a new strand is synthesized, the probes are displaced, the label cleaved off, and a fluorescent signal proportional to the amount of the cleaved probe is generated. The fluorescence is measured and recorded at each cycle of PCR. Cycle threshold (C_t) is defined as the fractional PCR cycle number in which the sample fluorescence signal reaches a level above an assigned fluorescence threshold. The Ct value indicates the beginning of the exponential amplification of the template DNA or RNA and is proportional to the concentration of the sample.

Bottom—A standard curve is generated using standards with known copy numbers. A linear graph (C_t vs. copy number) is generated which is used to determine the copy number of patient sample. Patient sample DNA/RNA generates certain Ct value corresponding to copy value.

Real-time PCR for bacterial endophthalmitis has been described using universal bacterial probe, gram-positive probe, and several bacterial genus-specific probes [15]. A combined use of SYBR Green 16S rDNA-based universal PCR (SGRU-PCR) and multiplex gram-specific *Taq*Man-based PCR (MGST-PCR) was found to having high sensitivity in bacterial detection in intraocular fluids. Fungal ribosomal DNA (28S rDNA) has been measured in ocular fluids by quantitative broad-range

real-time PCR in 76 patients with endophthalmitis, and the results were compared with 421 noninfectious controls [16]. Fungal 28S rDNA was detected in 11 of 76 infectious endophthalmitis patients (14.5%) with high copy numbers of fungal DNA (1.7×10^3 to 7.9×10^6 copies/ml) of which ten were confirmed to be fungal endophthalmitis and one was false-positive in the control group. Same group of authors have also shown the utility of 18S rDNA-based fungal real-time PCR in the diagnosis of *Candida* and *Aspergillus* uveitis/endophthalmitis [17].

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Chapter 26
Microbiology of Common Bacteria and Fungi

Savitri Sharma

Microbiology Spectrum

The microbiology spectrum in different clinical categories of endophthalmitis varies. Additionally, geographical location may influence the etiology of endophthalmitis. In postoperative endophthalmitis, the microbiology spectrum in Europe and the USA seem to be comparable [1, 2]. According to Endophthalmitis Vitrectomy Study [1], gram-positive bacteria were most commonly (94.2%) associated with culture-positive postoperative endophthalmitis, of which 70% isolates were coagulase-negative staphylococci, 9.9% *Staphylococcus aureus*, 9.0% *Streptococcus* spp., and 3% constituted other gram-positive bacteria. Gram-negative bacteria affected 5.9% of cases. Though dominated by gram-positive cocci, the spectrum of organisms includes higher incidence of gram-negative bacteria and fungi in postoperative endophthalmitis seen in Asian countries [3–6]. Cases with polymicrobial etiology have also been reported from some countries. With a rate of 0.05% post-cataract surgery endophthalmitis, one study from South India reported *Nocardia* spp. as the most common isolate between 2002 and 2003 [7]. The same authors have reported a cluster endophthalmitis caused by *Burkholderia cepacia* that was traced to the anesthetic eye drop used for surgery by genotyping [8]. *B. cepacia* has been reported to be associated in post-cataract surgery, posttrauma, and post-penetrating keratoplasty surgery endophthalmitis [9]. It seems to be associated with both acute and chronic clinical presentations. One case of recurrent endophthalmitis by *B. cepacia* has also been reported [10].

Similar to postoperative endophthalmitis, coagulase-negative staphylococci are the predominant pathogen in post-intravitreal injection endophthalmitis [11]. Less common organisms include *Streptobacillus* spp. and atypical mycobacteria.

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The incidence of post-penetrating keratoplasty endophthalmitis and post-vitrectomy is reported to be 0.5% and 0.45%, respectively [4, 12]. The microbiological spectrum is predominantly made up by gram-positive bacteria (*Staphylococcus* spp., *Enterococcus faecalis*) with some reports of gram-negative bacteria (*Pseudomonas* spp., *Klebsiella* spp.). In recent times *Klebsiella* spp., *Mycobacterium abscessus*, and *Candida parapsilosis* have been reported from endophthalmitis following Descemet stripping automated endothelial keratoplasty (DSAEK) surgery [13]. *Stenotrophomonas maltophilia* is an important pathogen, increasingly recognized for its role in endophthalmitis with wide range of risk factors such as trauma, cataract surgery, keratoplasty with keratitis, and vitreous lavage [14].

The incidence of post-trabeculectomy endophthalmitis ranges between 0.061 and 1.80% and is most commonly caused by α-hemolytic streptococci including *Streptococcus pneumoniae.* The second most common isolate from these cases is *Haemophilus influenzae*. The other reported organisms include *Staphylococcus aureus*, *Pseudomonas* spp., *Moraxella* spp., *Enterococcus faecalis*, *Propionibacterium acnes*, atypical mycobacteria, fungi, etc.

The common organisms associated with endophthalmitis following penetrating trauma of the eye with intraocular foreign body are *Bacillus* spp. and *Streptococcus* spp. [15]. In a large series of *Bacillus* endophthalmitis, 90.3% patients had trauma to the eye with or without retained intraocular foreign body [16]. *Bacillus* spp. are rarely associated with postoperative endophthalmitis. The spectrum of organisms associated with posttraumatic endophthalmitis is based on the type of injury, soiling of the wound, geographical location, first aid received by the patient, and immunity of the patient. *Clostridium* spp. may be involved in patients with road traffic accidents. A series of 67 posttraumatic endophthalmitis cases from Saudi Arabia showed coagulase-negative staphylococci and *Streptococcus* spp. accounting for infection in most cases, and the incidence of both was higher in patients with retained intraocular foreign body [17].

Polymicrobial infections are more commonly associated with posttraumatic endophthalmitis compared to postoperative endophthalmitis [18].

The prevalence of exogenous fungal endophthalmitis is higher in tropical countries. Prevalence of fungal etiology was found to be similar in a retrospective analysis of 182 posttraumatic and 206 postoperative endophthalmitis patients by Kunimoto et al., who suggested that the rate of fungal endophthalmitis is probably driven by climatic conditions rather than mechanism of injury [18]. *Fusarium* and *Aspergillus* spp. are the most common molds involved. A 14-year data on fungal endophthalmitis from a teaching eye institute in North India analyzed 113 patients of whom 53, 48, and 12 patients, respectively, were postoperative, posttraumatic, and endogenous endophthalmitis. *Aspergillus* species was the most common (54.4%) agent, followed by yeast (24.6%), and dematiaceous fungi (10.5%) [19].

The most common etiological agents of bacterial endogenous endophthalmitis are *Streptococcus* spp. and *Staphylococcus aureus* [20]. Alpha-hemolytic streptococci including *Streptococcus pneumoniae* are common causes secondary to meningitis and endocarditis. Endogenous endophthalmitis with β-hemolytic *Streptococcus* (Group G) have been correlated with skin wound and malignancy, while Group B β-hemolytic *Streptococcus* has been found in neonatal meningitis

patients. While gram-positive organisms predominate, there are several other types of organisms that may cause endogenous endophthalmitis.

Although rare, *Nocardia asteroides*, a weakly acid fast organism, and *Mycobacterium tuberculosis*, a strongly acid fast organism, may disseminate from pulmonary focus and cause endogenous endophthalmitis [21]. *Candida albicans* followed by *Aspergillus* spp. are the most common causes of fungal endogenous endophthalmitis. These are reported mostly in immunosuppressed patients, patients with organ transplants, leukemia, or intravenous drug abusers. Other organisms that may find their way to the eye and cause endophthalmitis during a systemic infection include *Toxoplasma gondii* and *Toxocara canis*. Clinically these organisms may produce severe posterior endophthalmitis with focal retinochoroiditis and satellite lesions.

Microbiological Features of Common Bacteria and Fungi Causing Endophthalmitis

Bacteria

Staphylococcus species

Staphylococci belong to the family *Micrococcaceae* that include two genera—*Staphylococcus* and *Micrococcus*. Staphylococci are gram-positive cocci that occur in grape-like clusters (Fig. 26.1 left), ferment glucose, and are catalase positive. They are ubiquitous and are the most common cause of localized suppurative lesions in man. There are more than 20 species of which *Staphylococcus aureus* is most virulent. Apart from golden yellow colonies (Fig. 26.1 right),

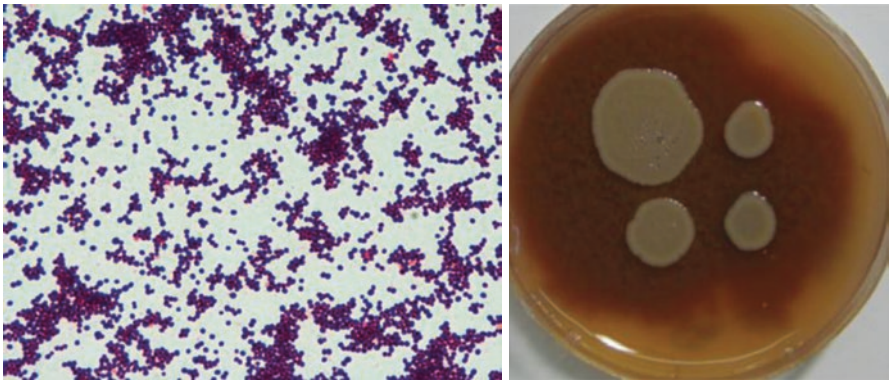

Fig. 26.1 S*taphylococcus aureus. Left*—culture smear showing gram-positive cocci in pairs, short chains, and clusters (*S. aureus*, Gram stain, ×1000); *right*—blood agar showing heavy growth of opaque, golden yellow colonies of *S. aureus*

S. aureus consistently produces the enzyme coagulase and ferments mannitol. Coagulase-negative staphylococci are often part of commensal flora of the human skin and mucus membrane including the conjunctival sac and are usually less pathogenic. While ample evidence of causative role of staphylococci in dacryocystitis, keratitis, and endophthalmitis is available, their role in blepharitis, marginal keratitis, phlyctenulosis, etc. is not so clear. The sources of infection are usually own flora or other human patients and carriers; inanimate objects are less important. Patients with superficial infections and respiratory infections disseminate the organisms in large numbers in the environment. As mentioned earlier, coagulase-negative staphylococci are the most common cause of postoperative endophthalmitis in the world. Nosocomial (hospital acquired) infections can be minimized by (1) isolation of patients with open staphylococcal lesions, (2) detection of staphylococcal lesions among hospital staff, (3) strict aseptic precautions in the operating rooms and wards, and (4) hand hygiene practice by hospital staff while handling patients.

Laboratory diagnosis is usually simple as staphylococci grow abundantly on media such as blood agar, chocolate agar, nutrient agar, and many other media. Characteristic colonies coupled with a few biochemical reactions are adequate to differentiate *S. aureus* from coagulase-negative staphylococci. Accurate identification of coagulase-negative staphylococci is aided by currently available automated methods such as VITEK 2 compact system from bioMérieux, France.

Drug resistance is common among staphylococci, the first resistance developing against penicillin in 1940s. Methicillin was the first compound introduced to combat resistance to penicillin; however, soon methicillin-resistant *Staphylococcus aureus* (MRSA) emerged that exhibited resistance to many other antibiotics. Currently, vancomycin is the most effective antibiotic.

Streptococcus species

Streptococci are gram-positive cocci that occur in pairs and short or long chains, catalase negative, and nutritionally fastidious; they require blood-enriched media for growth. There are several systems of classification of streptococci, and one of them is based on hemolysis (beta-complete hemolysis, alpha-partial hemolysis with greenish discoloration, gamma-no hemolysis) on sheep or horse blood agar. One of the most important ophthalmic pathogens includes *Streptococcus pneumoniae*, also known as *Diplococcus pneumoniae* (Pneumococcus), which is typically lanceolate shaped, capsulated occurring in pairs (Fig. 26.2 left), alpha-hemolytic on blood agar, tiny, transparent or translucent on chocolate agar with greenish discoloration (Fig. 26.2 right), and susceptible to optochin (ethyl hydrocuprein). Other alpha-hemolytic streptococci (optochin resistant) are collectively known as "viridans streptococci" that constitute several species, which are normal commensal in the throat but are potentially opportunistic pathogens. Differentiation of the species and antibiotic susceptibility testing is important as alpha-hemolytic streptococci have been reported to be resistant to aminoglycosides, penicillins, and fluoroquinolones [22].

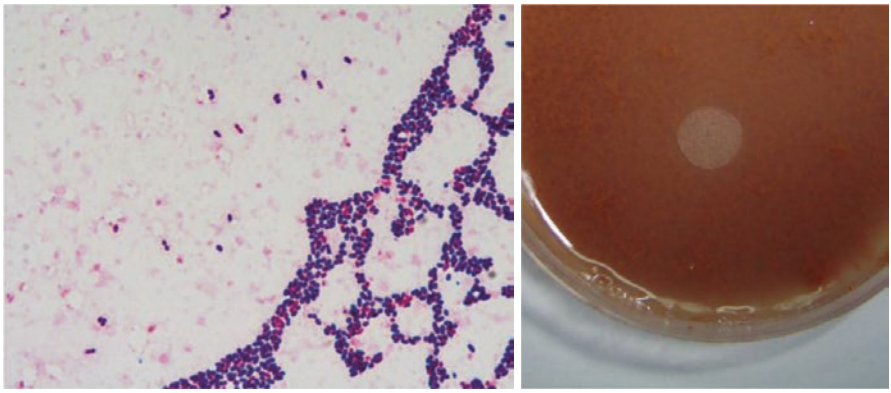

Fig. 26.2 *Streptococcus*. *Left*—culture smear of *Streptococcus pneumoniae* showing gram-positive elongated (lanceolate shaped) cocci in pairs with mild capsule (Gram stain, ×1000); right—chocolate agar showing tiny translucent confluent colonies of *Streptococcus pneumoniae* grown in a vitreous drop (37 °C, 2 days)

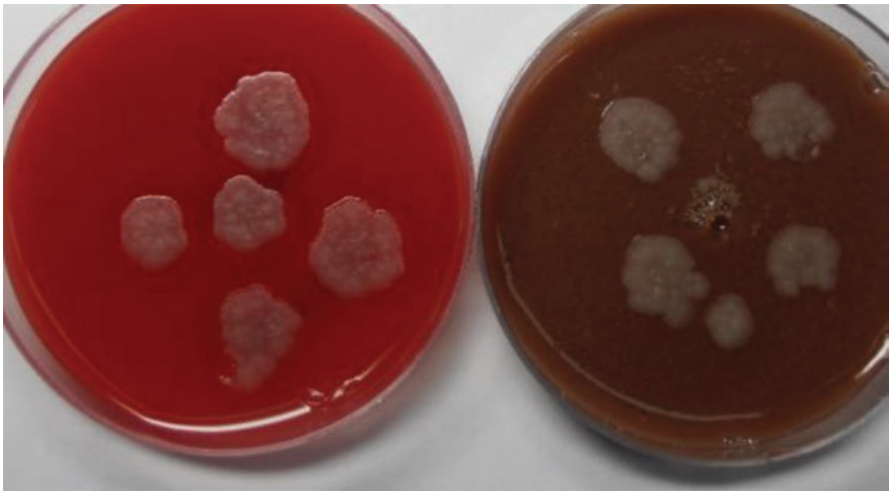

Fig. 26.3 *Bacillus*. Sheep blood agar (*left*) and chocolate agar (*right*) showing rough, dirty yellow, translucent, flat colonies of *Bacillus cereus* grown in vitreous drops (37 °C, 2 days)

Bacillus species

The genus *Bacillus* includes several species of gram-positive, large, thick, often beaded, spore-forming bacilli that grow on ordinary media producing rapidly growing large colonies (Fig. 26.3 left). They are ubiquitous and most common laboratory contaminants. *Bacillus cereus* is the most common pathogen. Species identification requires VITEK system or other automated methods. They are known to be associated with severe posttraumatic endophthalmitis [16]. They are susceptible to vancomycin, clindamycin, and several aminoglycosides.

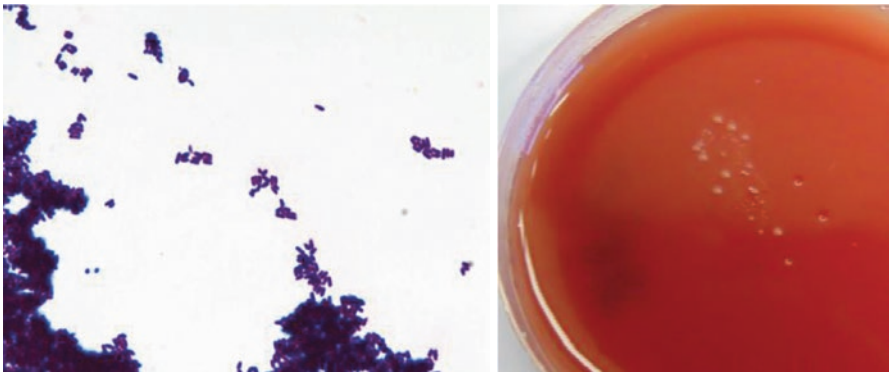

Fig. 26.4 *Left*—culture smear of *Corynebacterium* species showing gram-positive bacilli arranged in Chinese letter pattern (Gram stain, ×1000); *right*—sheep blood agar showing tiny, yellowish raised, translucent, nonhemolytic colonies of *Corynebacterium amycolatum* grown in vitreous drops (37 °C, 3 days)

Corynebacterium and *Propionibacterium* species

Corynebacterium and *Propionibacterium* are two genera that are similar in many respects except that the former is aerobic and the latter is anaerobic. Several species have been reported as normal commensals in the conjunctival sac and lid margins. They are low virulent organisms associated with chronic endophthalmitis. Joseph et al. have reported a series of 16 cases of *Corynebacterium* endophthalmitis, and the clinical setting included trauma, cataract surgery, and penetrating keratoplasty surgery [23]. *Corynebacterium* and *Propionibacterium* are small gram-positive bacilli that are arranged in Chinese letter pattern (palisades, L and V shapes—Fig. 26.4 left), non-motile, catalase positive, and ferment carbohydrates. *Corynebacterium* produce lactic acid and *Propionibacterium* produce propionic acid. Both organisms grow slowly and require enriched media for growth and special biochemical tests to identify species. They are usually susceptible to various groups of antibiotics. Tiny, raised, translucent, nonhemolytic colonies of *Corynebacterium* species grown in vitreous sample are seen in Fig. 26.4 (right).

Nocardia and *Mycobacterium* species

Nocardia species are strict aerobic gram-positive, beaded, branching filamentous bacteria that may break into short bacilli (Fig. 26.5 left). They may appear as gram-negative filaments with gram-positive beads and are acid fast with weak acid (1% H_2SO_4) in modified Ziehl-Neelsen stain (Kinyoun stain) owing to mycolic acid in their cell wall. The colonies on blood and chocolate agar are often chalky white and dry (Fig. 26.5 right). They occur as saprophytes in nature and have been reported from posttraumatic as well as postoperative endophthalmitis [24]. Amikacin is the drug of choice although the organism is susceptible to many other antibiotics. MALDI-ToF mass spectrometry is more reliable than biochemical reactions in species identification.

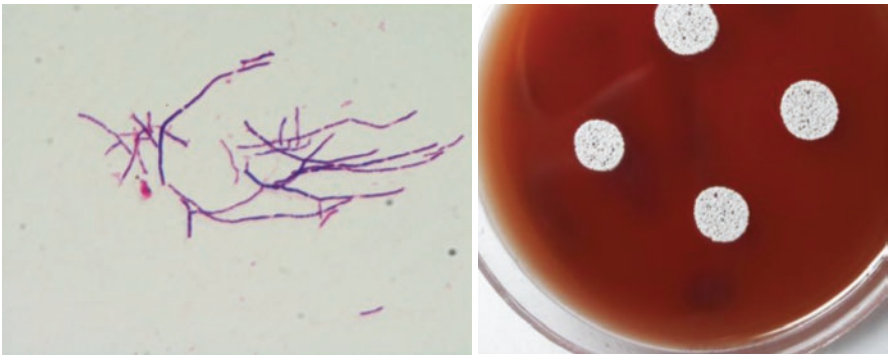

Fig. 26.5 *Left*—gram-positive, thin, beaded, branching filaments of *Nocardia asteroides* (Gram stain, ×1000); *right*—tiny, chalky white, nonhemolytic colonies of *Nocardia asteroides* on sheep blood agar grown in vitreous drops (37 °C; 4 days)

Mycobacterium tuberculosis is a rare cause of endogenous endophthalmitis [25]. Ocular infections are more commonly caused by atypical mycobacteria. *M. chelonae* and *M. manitobense* endophthalmitis are microbiologically challenging to diagnose [26, 27]. DNA sequencing was applied for the identification of *M. manitobense* cultured from vitreous of a patient with post-cataract surgery endophthalmitis [27].

Mycobacteria are gram-positive, slender, beaded bacilli that stain poorly with gram stain but are strongly acid fast in Ziehl-Neelsen stain. In contrast to *M. tuberculosis*, atypical mycobacteria are rapid growers and grow within 7 days on regular laboratory media such as blood agar and chocolate agar. Biochemical tests or molecular methods may help identify the species; VITEK cards are not available for *Mycobacterium* and *Nocardia* species identification. In recent times MALDI-ToF mass spectrometry has emerged as an useful tool for species identification.

Pseudomonas species and *Burkholderia cepacia*

Pseudomonads are saprophytic, ubiquitous, usually slender, gram-negative bacilli (Fig. 26.6 left). Unlike *Enterobacteriaceae* family members such as *Klebsiella* species and *Escherichia coli*, they are non-fermenters of sugars and oxidase positive. They are a common cause of endophthalmitis and are dreaded agent of cluster endophthalmitis. Most members possess potent virulence factors (enzymes and toxins) and can destroy tissues rapidly. *P. aeruginosa* is very virulent.

Pseudomonads can utilize a variety of compounds for nutrition and grow even in distilled water. They produce non-lactose-fermenting colonies on MacConkey's agar and utilize citrate, and most species are motile. VITEK 2 compact system is very reliable for species determination. *P. aeruginosa* often produces large, gray, moist colonies with greenish pigment and beta-hemolysis on blood agar (Fig. 26.6 right).

Antimicrobial resistance among *P. aeruginosa* is a global concern. Nosocomially acquired isolates tend to be more resistant than community-acquired strains. Several

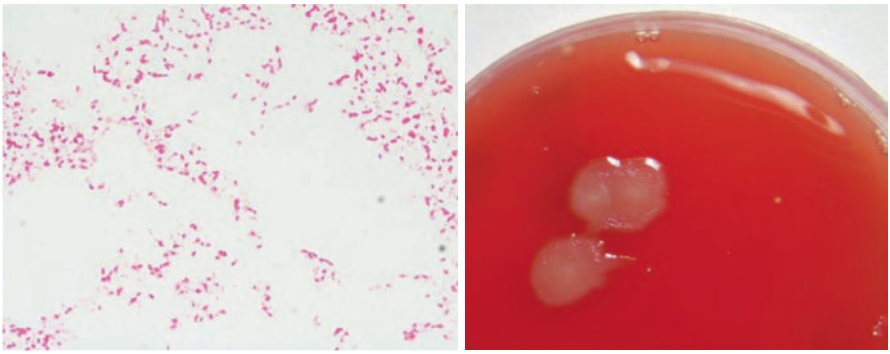

Fig. 26.6 *Left*—slender gram-negative bacilli in culture smear of *Pseudomonas aeruginosa* (Gram stain, ×1000); right—large, flat, moist, greenish colonies of *P. aeruginosa* grown in the inoculum of vitreous on sheep blood agar (37 °C; 2 days)

mechanisms such as mutations in genes encoding porins, efflux pumps, penicillin-binding proteins, and chromosomal beta-lactamase contribute to the resistance. In addition *P. aeruginosa* strains may contain extended spectrum beta-lactamases and metallo-beta-lactamases that can degrade imipenem. Rise in multidrug-resistant *P. aeruginosa* has resulted in revisiting the use of toxic drugs like colistin and polymyxin B.

Burkholderia is a new genus that has emerged out of nomenclatural rearrangement of the genus *Pseudomonas* based on rRNA homology. rRNA group II pseudomonads were reclassified as *Burkholderia* and *Ralstonia* [28].

Members in these groups are environmental bacteria that can be pathogenic to humans, animals, and plants. *B. cepacia* has emerged as an important human pathogen in the last decade. *Burkholderia* species can be recovered on most primary isolation media used in clinical laboratories. Identification of *B. cepacia* using conventional biochemical tests may be difficult. VITEK 2 compact system is useful for identification. Several molecular approaches have been described for specific identification.

Burkholderia cepacia is resistant to several antibiotics. While susceptibility to imipenem and meropenem is variable, the organism is usually susceptible to piperacillin and ceftazidime. Specific interpretative criteria are not available for susceptibility testing, and those available for *Pseudomonas* are applied. Minimum inhibitory concentration testing by microbroth dilution method or E test is considered more reliable than disc diffusion testing.

Klebsiella species, *Escherichia coli*, and *Enterobacter* species

These gram-negative, nonspore-forming bacilli belong to the family *Enterobacteriaceae*—a large family of 27 genera and more than 110 species. Characteristic features of the species include aerobic and facultative anaerobic growth on regular media, fermentation of glucose, nitrate reductase positive,

catalase positive, and oxidase negative. They may be associated with posttraumatic endophthalmitis or endogenous endophthalmitis following septicemia.

High level of antibiotic resistance to multiple drugs and intrinsic resistance to certain drugs is common in this group of organisms. Many of them are reported to harbor extended spectrum beta-lactamases (ESBL), cephalosporinases, and carbapenemases. The prevalence of ESBL and AmpC beta-lactamase-mediated resistance was found to be 7% and 18.5%, respectively, among ocular isolates of *E. coli* and *Klebsiella pneumoniae* [29]. Susceptibilities may vary from isolate to isolate even within a genus; therefore, treatment based on susceptibility test results is recommended rather than following empirical guidelines.

Haemophilus influenzae

Members of the genus *Haemophilus* are gram-negative, non-motile, nonspore-forming oxidase-positive small coccobacilli or filamentous rods that are obligate parasites exclusively adapted to human respiratory tract and form a part of the normal flora. They are facultative anaerobes and require growth factors X (hemin) and/or V (nicotinamide adenine dinucleotide) present in blood for growth. They grow best on sheep blood chocolate agar. *H. influenzae* produces small, translucent, grayish, smooth, flat-convex, occasionally mucoid colonies owing to capsule and a characteristic "mousy nest" odor. In clinical samples they are often found intracellularly. Ocular infections are usually endogenous. Differentiation of *H. influenzae* from other species is difficult using standard laboratory tests, and automated methods such as VITEK 2 or API are helpful.

Unexposed to antibiotics, wild-type stains of *Haemophilus* spp. are usually susceptible to several groups of antibiotics; however, large proportion of clinical isolates may be found resistant to ampicillin, beta-lactam antibiotics, chloramphenicol, and tetracyclines.

Fungi

Aspergillus *and* Fusarium *species*

Similar to other opportunistic moniliaceous molds, both *Aspergillus* and *Fusarium* species occur as saprobes in soil, air, and plant litter and are plant and human pathogens. The spectrum of disease in humans is largely determined by the local and general immunologic and physiologic state of the host. In most cases the portal of entry is a break in the epithelium or by the respiratory passage. Several species of *Aspergillus* and *Fusarium* are known to cause both endogenous and exogenous endophthalmitis. Members of both of these genera grow rapidly on common laboratory media although characteristic colonies and pigments are formed on Sabouraud

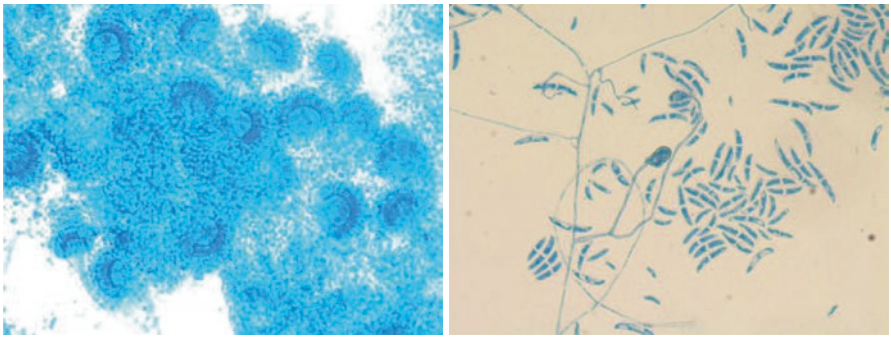

Fig. 26.7 Microscopic examination of fungal cultures in lactophenol cotton blue stain showing characteristic spores of (*left*) *Aspergillus fumigatus* and (*right*) *Fusarium solani*

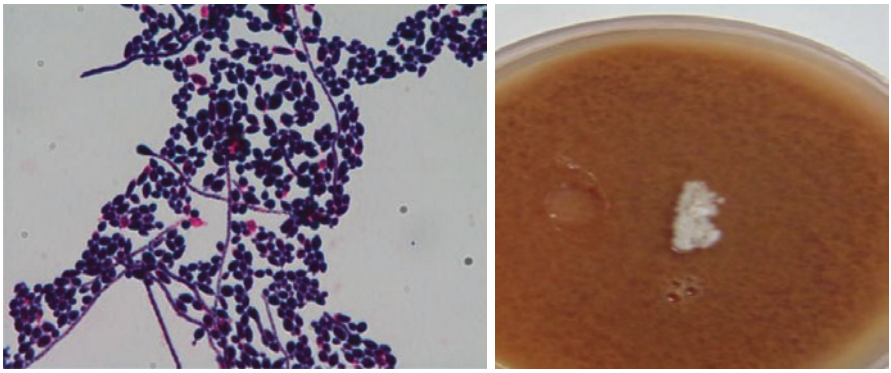

Fig. 26.8 *Left*—budding yeast cells and pseudo and true hyphae of *Candida ciferrii* (currently renamed as *Stephanoascus ciferrii*) in culture smear (Gram stain, ×1000). *Right*—white, smooth, raised colonies of *Candida ciferrii* on and around the capsular bag on chocolate agar after 48 h of incubation at 37 °C. Intraocular lens with no growth is seen to the left of capsular bag on chocolate agar

dextrose agar or potato dextrose agar. Vegetative asexual spores that help in identification are formed only in culture (Fig. 26.7). Left and right show the microscopic morphology of *Aspergillus fumigatus* and *Fusarium solani*, respectively. Apart from morphological identification, fungi are often identified by molecular methods, notably DNA sequencing.

Candida *species*

Yeasts are unicellular fungi, which occur as spherical or ellipsoidal cells and reproduce by simple budding. *Cryptococcus neoformans* is the only pathogenic yeast. *Candida albicans* is a yeast-like fungus that grows partly as yeast and partly as elongated pseudo or true septate hyphae (Fig. 26.8 left). *Candida* species can grow on several standard media in the laboratory and produce white or cream raised

smooth paste-like colonies (Fig. 26.8 right). Most species can grow at 27 °C and 37 °C. Simple tests such as pellicle on the surface of Sabouraud glucose broth, urease test, and germ tube test are used to differentiate *C. albicans* from other species; however, accurate identification requires VITEK 2 compact system or MALDI-ToF automated techniques. DNA sequencing has also been applied for the purpose. Most yeasts are susceptible to amphotericin B. Resistance to azoles may be found in some isolates.

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Chapter 27
Trend and Challenges of Antimicrobial Susceptibility of Bacteria and Fungi Causing Endophthalmitis: A Microbiological Perspective on Global Trends

Joveeta Joseph, Bhavani Sontam, and Savitri Sharma

Prevention and elimination of endophthalmitis are a constant goal of every ophthalmic surgeon. Today virtually every surgeon follows a standard of care that involves antisepsis and antibiotics without knowing exactly the reason (why), the modality (how), and the precise time (when) to intervene with effective prophylactic measures [1]. The introduction of various antimicrobials for treating a variety of infections was the reason for performing antimicrobial susceptibility testing as a routine procedure in all microbiology laboratories. Pharmacokinetics and spectrum of activity of antimicrobial intravitreal drugs are an important consideration. Dose, pH, ionization, protein binding, and route of entry also affect the drug concentration. Ocular factors such as the surgical status of the eye, the presence or absence of lens and vitreous, and degree of breakdown of the blood retinal barrier are the host factors to consider [2]. The microbial spectra and susceptibility patterns have exhibited variations over time and differ according to geographic location, population, and ethnic groups. Because of the rapidly progressive nature of endophthalmitis, it is important to monitor the microbial spectra and antibiotic susceptibilities at the local level through periodic analyses to ensure that empirical therapy remains appropriate [1]. The results of in vitro antibiotic susceptibility testing guide clinicians in an appropriate selection of initial empiric regimens and the drugs used for individual patients in specific situations. The selection of an antibiotic panel for susceptibility testing is based on the commonly observed susceptibility patterns and is revised periodically. In the present chapter, we have reviewed the global trends in the last few decades in the changes in antibiotic susceptibility patterns for bacteria and fungi causing endophthalmitis.

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Antimicrobial Susceptibility Testing

Principle

Antimicrobial susceptibility tests (ASTs) basically measures the ability of an antimicrobial agent to inhibit the in vitro microbial growth. In ASTs, the antimicrobial contained in a reservoir is allowed to diffuse out into the medium and interact in a plate freshly seeded with the test organisms. There are many different procedures to study the effects of various antimicrobial agents, and Mueller-Hinton agar (MHA) is considered best for routine susceptibility testing since it is has batch-to-batch reproducibility and low concentration of inhibitors of sulfonamide, trimethoprim, and tetracyclines and produces satisfactory results for most non-fastidious pathogens. Fastidious organisms that require specific growth supplements need different media to grow for studying the susceptibility patterns. The disk diffusion method of AST is the most practical method and is still the method of choice for the average laboratory. Automation may force the method out of the diagnostic laboratory, but in India (and in similar economy countries) as well as in the smaller laboratories of even advanced countries, it will certainly be the most commonly carried out microbiological test for many years to come [3].

Factors Influencing Antimicrobial Susceptibility Testing

pH: Each batch of agar medium should have a pH of 7.2–7.4. If the pH of the medium is too low, certain drugs such as aminoglycosides, quinolones, and macrolides lose their potency. The antibiotic classes such as tetracyclines appear to have excess activity at a lower pH, and the vice versa happens in the case of the higher pH [4].

Moisture: The presence of moisture content on the medium can counteract with accuracy of the susceptibility testing [4].

Effects of medium components: If the media selected for the antibiotic susceptibility contain excessive amounts of thymine or thymidine compounds, they will reversibly inhibit the action of certain antimicrobial agents such as trimethoprim groups. This reversible inhibition yields smaller or less distinct or even no zones and will be misinterpreted as resistant antibiotics. MHA is low in thymine and thymidine content, and it can be used successfully to study the susceptibility of antibiotics. Also the medium containing excessive cation reduces the zone size, while low cation content results in unacceptably large inhibition zones [4].

Methods of Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing methods are divided into types based on the principle applied in each system [3]. They include the following (Table 27.1).

Table 27.1 Antimicrobial susceptibility testing methods

Diffusion	Dilution	Diffusion and dilution
Stokes method	MIC method 1. Broth dilution 2. Agar dilution	E test method
Kirby-Bauer method		

MIC: Minimum inhibitory concentration

Selection of the appropriate method will depend on the intended degree of accuracy, convenience, urgency, availability of resources, availability of technical expertise, and cost.

Diffusion Methods

The Kirby-Bauer and Stokes methods are usually used for antimicrobial susceptibility testing; the Kirby-Bauer method is recommended by the Clinical and Laboratory Standards Institute (CLSI, formerly, NCCLS). CLSI is an international, interdisciplinary, nonprofit, nongovernmental organization composed of medical professionals, government, industry, healthcare providers, educators, etc. which promotes accurate AST and appropriate reporting by developing standard reference methods, by indicating interpretative criteria and quality control parameters for standard test methods. Interpretative criteria of CLSI are developed based on the international collaborative studies; they are well correlated with MICs and the clinical data. Based on study results, CLSI interpretative criteria are revised frequently. CLSI is approved by FDA-USA and recommended by the World Health Organization (WHO) [3].

The Kirby-Bauer test is a qualitative assay, whereby disks of filter paper pre-impregnated with a standard concentration of a particular antibiotic are lightly pressed onto the agar surface. The test antibiotic immediately begins to diffuse outward from the disks, creating a gradient of antibiotic concentration in the agar such that the highest concentration is found close to the disk with decreasing concentrations further away from the disk. After an overnight incubation, the bacterial growth around each disk is observed. If the test isolate is susceptible to a particular antibiotic, a clear area of "no growth" is observed around that particular disk [4]. The zone around an antibiotic disk that has no growth is referred to as the "zone of inhibition" (Fig. 27.1), since this approximates the minimum antibiotic concentration sufficient to prevent growth of the test isolate. This zone is then measured in mm and compared to a standard interpretation chart of Tables 2A through I (Zone Diameter Interpretative Standards and Equivalent Minimum Inhibitory Concentration Breakpoints) of the NCCLS M100-S12, Performance Standards for AST, and the organisms are reported as either susceptible, intermediate, or resistant to the agents that have been tested [5].

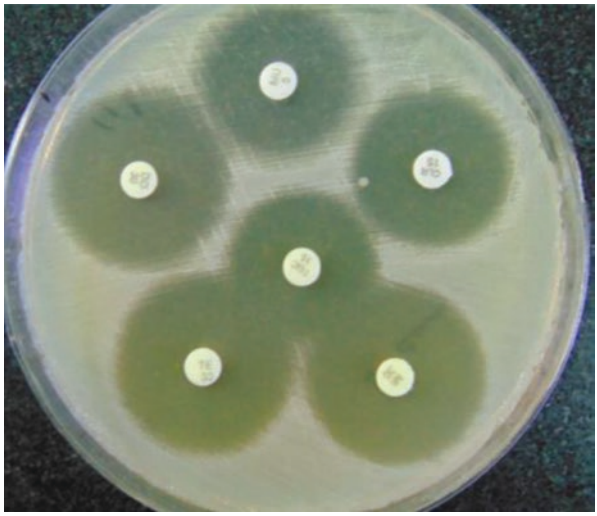

Fig. 27.1 Mueller-Hinton agar plate for susceptibility testing of *Staphylococcus* species to various antibiotics after an incubation period of 24 h by disk diffusion method. The diameter of the clear zone around each drug indicates whether the test organism is susceptible or not

Dilution Methods

The Broth dilution method involves subjecting the isolate to a series of concentrations of antimicrobial agents in a broth environment. Microdilution testing uses about 0.05–0.1 mL total broth volume and can be conveniently performed in a microtiter plates. Macrodilution testing uses broth volumes at about 1.0 mL in standard test tubes. For both of these broth dilution methods, the lowest concentration at which the isolate is completely inhibited (as evidenced by the absence of visible bacterial growth) is recorded as the minimal inhibitory concentration or MIC [3].

A procedure similar to broth dilution is agar dilution. Agar dilution method follows the principle of establishing the lowest concentration of the serially diluted antibiotic concentration at which bacterial growth is still inhibited [3].

Dilution and Diffusion Methods

E test, also known as the Epsilometer test, is an "exponential gradient" testing methodology where the "E" refers to the Greek symbol "epsilon" (ε). The E test which is a quantitative method for antimicrobial susceptibility testing applies to both the dilution of antibiotic and diffusion of antibiotic into the medium. It utilizes a plastic test strip impregnated with a gradually decreasing concentration of a particular antibiotic. The strip also displays a numerical scale that corresponds to the antibiotic concentration contained therein. Following the incubation, a symmetrical inhibition ellipse is produced (Fig. 27.2). The intersection of the inhibitory zone edge and the calibrated carrier strip indicates the MIC value over a wide concentration range (>10 dilutions) with inherent precision and accuracy [3]. This method provides for a convenient quantitative test of antibiotic resistance of a clinical isolate. However, a separate strip is needed for each antibiotic, and therefore the cost of this method could be high.

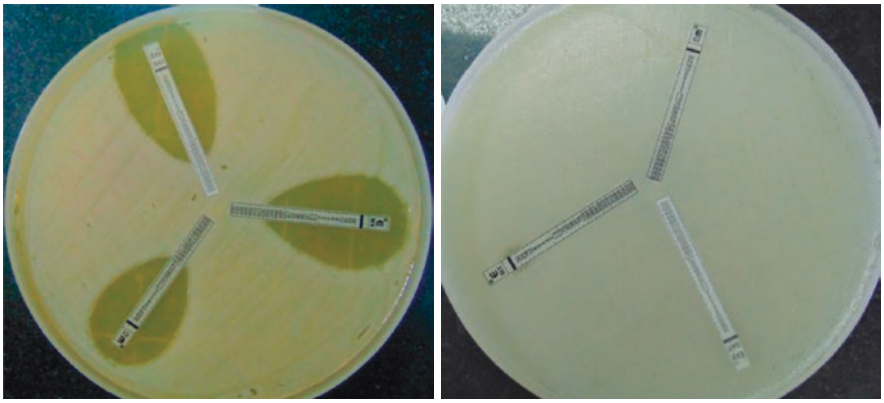

Fig. 27.2 Mueller-Hinton agar plate for susceptibility testing of *Staphylococcus* species to various antibiotics after an incubation period of 24 h by E test method. (*Left*) The inhibition ellipse is produced and the intersection of the inhibitory zone edge and the calibrated carrier strip indicates the MIC against each drug. (*Right*) No inhibitory zone around the strip signifies complete resistance of the isolate to the test drug

Changing Trends in Antibacterial Susceptibility Profile

The earliest reports of susceptibility testing in endophthalmitis included mainly case reports and the panel of drugs tested. Mark and Gaynon reported a case of *Acinetobacter anitratus* endophthalmitis in 1983 [6]; this patient was treated with penicillin, but the infection did not respond. It was then found that the organism was sensitive in vitro to gentamicin, tobramycin, kanamycin, and amikacin; it was intermediately sensitive to carbenicillin and resistant to penicillin. These early reports paved the way for a larger series, thus establishing the evidence for adequate treatment of both gram-positive and gram-negative organisms in confirmed cases of endophthalmitis.

Gram-Positive Bacteria

Global Perspective

Davis et al. suspected a change in the expected sensitivity of coagulase-negative staphylococci when three cases of endophthalmitis due to multiple resistant organisms failed to respond to intravitreal cefazolin and gentamicin [7]. On reviewing their records from 1973 to 1986, they found increased resistance to gentamicin and methicillin. No isolates were resistant to vancomycin. The Endophthalmitis Vitrectomy Study (EVS, February 1990 to January 1994) that recruited patients with acute bacterial endophthalmitis corroborated this observation [8]. In the EVS, all gram-positive organisms were susceptible to vancomycin (100%). Susceptibilities of coagulase-negative micrococci in decreasing order were as follows: amikacin,

86.1%; ciprofloxacin, 77.9%; oxacillin, 62.7%; and ceftazidime, 62.1%. Corresponding susceptibilities of "other" gram-positive organisms in decreasing order were: ceftazidime, 74.3%; ciprofloxacin, 67.6%; oxacillin, 60.0%; and amikacin, 49.3%. In addition, all of five isolates of *Streptococcus pneumoniae* tested were susceptible to ceftazidime.

Benz et al. reviewed the 5-year (1996–2001) microbiology records of patients with culture-proven endophthalmitis at the Bascom Palmer Eye Institute [9] and found that among the 246 gram-positive organisms identified, the sensitivities were the following: vancomycin 100%, gentamicin 78.4%, ciprofloxacin 68.3%, cefazolin 66.8%, and ceftazidime 63.6%. During the period of the study, 1996–2001, there was a significant decrease in the sensitivity of gram-positive organisms to ciprofloxacin (from 72% in 1996, to 36% in 2001). Although levofloxacin showed better activity in 2001 against gram-positive isolates than ciprofloxacin (62% vs. 36%), it still had incomplete gram-positive coverage. In comparison, during the same period sensitivities of gram-positive isolates to gentamicin remained relatively stable. The widespread and routine use of third-generation fluoroquinolones as therapeutic and prophylactic medications in North America may have led to an increase in microbial resistance against them. The difference from the EVS study could be due to geographic differences [8], as well as the inclusion criteria in EVS acute-onset endophthalmitis associated with cataract surgery or secondary intraocular lens placement versus all categories of endophthalmitis. Similarly, Recchia et al. reviewed post-cataract surgery endophthalmitis data in the Wills Eye Hospital for 11 years, 1989–2000, and reported statistically significant resistance of gram-positive bacteria to ciprofloxacin and resistance of coagulase-negative staphylococci to ciprofloxacin (20–38%) and cefazolin (19–40%) [10]. Resistance to bacitracin, trimethoprim-sulfamethoxazole, and vancomycin remained statistically unchanged; 30% of all isolates (and 35% of coagulase-negative staphylococci) were resistant to ofloxacin [8].

A 25-year review of culture-positive endophthalmitis collected from 1987 to 2011 at the New York Eye and Ear Infirmary by Gentile and co-workers have documented a statistically significant decrease in microbial susceptibility over time for ampicillin, cefazolin, cefotetan, cephalothin, ceftriaxone, clindamycin, erythromycin, and methicillin/oxacillin [11].They also observed an increase in susceptibility to gentamicin, imipenem, and tobramycin. Susceptibility to fluoroquinolones for all isolates ranged from a low 67% for levofloxacin to a high 81% for gatifloxacin during the time period from 2000 to 2011. Only levofloxacin showed a decrease in microbial susceptibility that approached significance. Vancomycin displayed 99.7% susceptibility against 727 gram-positive isolates, and 99.3% (143/144) susceptibility was observed for linezolid (approved by the Food and Drug Administration only in 2000).

Similar studies outside the USA, conducted at the Federal University of São Paulo, Brazil from 2006 to 2009, showed that 79.5% and 89.5% of coagulase-negative staphylococci (CoNS) were sensitive to gatifloxacin and moxifloxacin, respectively [12]. Additionally, most fourth-generation quinolone-resistant samples were also methicillin resistant. In a previous report from the same institute, 2000 to 2005, all CoNS (100%) were susceptible to both moxifloxacin and gatifloxacin [13]. Falavarjani et al. at Tehran studied the antibiotic resistance in 21 culture-proven

endophthalmitis cases; resistance to penicillin G (7 isolates), oxacillin (5 isolates), clindamycin (4 isolates), cefazolin (2 isolates), ceftazidime (5 isolates), ciprofloxacin (2 isolates), ceftriaxone (2 isolates), and imipenem (1 isolate) [14]. There was no resistance to vancomycin.

A retrospective analysis on 912 cases of post-traumatic endophthalmitis at Zhongshan Ophthalmic Center, Guangzhou, China, from 1990 to 2009 showed that *S. epidermidis* had the greatest susceptibility to ceftazidime (90.7%), followed by cefuroxime (88.9%), but showed at least some resistance to all other antibiotics tested [15]. *S. saprophyticus* was highly susceptible to ceftazidime (100%) and cefuroxime (100%), followed by ciprofloxacin (from 93.3% to 96.4%, $p > 0.05$). *B. subtilis* showed susceptibility (100%) to ciprofloxacin, gentamicin, ofloxacin, cefuroxime, and ceftazidime. However, there was a variation of antibiotic susceptibility analysis among the isolates between the different time periods. During the first decade (1990–1999), ciprofloxacin was the most effective antibiotic against bacterial isolates, followed by cefoperazone. For the second decade (2000–2009), ceftazidime showed the greatest level of activity against most bacterial isolates, followed by cefuroxime. Neomycin showed little activity against most bacterial isolates, except *B. subtilis*, which was highly sensitive to all the tested antibiotics except erythromycin and ampicillin. All cases with culture-proven endophthalmitis from the Eye, Ear, Nose, and Throat Hospital, Shanghai Medical College, between April 2004 and April 2014 were examined [16]. The authors found that 97.6% of 369 gram-positive isolates were sensitive to vancomycin. Three *B. cereus* isolates and six isolates of *Streptococcus* species were resistant to vancomycin. One hundred percent of the isolated staphylococcal species were susceptible to vancomycin. The other antibiotic susceptibilities were as follows: levofloxacin, 85.1%; gentamicin, 78.7%; rifampin, 77.2%; ofloxacin, 77.2%; chloramphenicol, 76.4%; and ciprofloxacin, 73.7%.

Indian Perspective

In the Indian subcontinent, the earliest reports were from the Endophthalmitis Research Group at the L.V. Prasad Eye Institute in Hyderabad, India. They reported microbiological profile of post-traumatic and postoperative endophthalmitis in the period 1991–1997 [17, 18]. In traumatic endophthalmitis, the gram-positive cocci were most susceptible to cefazolin (93.4%) and ciprofloxacin (93.2%), and gram-positive bacilli were most susceptible to ciprofloxacin (100%). In postoperative endophthalmitis, the gram-positive isolates were most susceptible to cefazolin (93.1%) followed by ciprofloxacin (86%); the gram-positive bacilli were 100% susceptible to several antibiotics, including vancomycin.

A study from Chennai, between 1995 and 1998, showed that among the gram-positive bacteria tested, 41/53 (77.3%) were sensitive to gentamicin, and 47/53 (88.6%) to cefotaxime, 88.4% (46/52) to ciprofloxacin, 92.6% (38/41) to cefazolin, and 72.9% (27/37) to ceftazidime [19]. All the gram-positive bacteria (100%) were

sensitive to vancomycin. The resistance of gram-positive bacteria to ceftazidime and ciprofloxacin was comparatively lower than the EVS results. Contradicting to these reports is a study by Vedantham et al. from Madurai [20]. In a series of 42 post-traumatic endophthalmitis managed at the Aravind Eye Hospital (January 2000–December 2001), majority of the organisms were susceptible to chloramphenicol and ciprofloxacin, and the susceptibility to vancomycin and amikacin was poor. Resistance of this magnitude to vancomycin and amikacin has not previously been reported in the literature. Another retrospective analysis of culture-proven endophthalmitis treated at the Aravind Eye Hospital, Tirunelveli, South India, over a 10-year period, 1997–2006, showed that the highest percentage of gram-positive cocci were susceptible to both cefazolin (100%) and moxifloxacin (100%) followed by chloramphenicol (98.3%), vancomycin (96.6%), and gatifloxacin (95.3%) [21]. The gram-positive bacilli were completely susceptible to amikacin and to all four tested fluoroquinolones, ciprofloxacin, ofloxacin, gatifloxacin, and moxifloxacin. Amikacin, gatifloxacin, and moxifloxacin also showed 100% sensitivity against *Nocardia* spp. of endophthalmitis isolates.

The susceptibility patterns of isolates from patients with exogenous endophthalmitis, January 2003–December 2013, at a tertiary eye care referral hospital of the Northeast India were slightly different [22]. While all the gram-positive bacteria were sensitive to vancomycin, only 54.5% showed sensitivity to amikacin and 45.5% to cefotaxime (33.3%). Sensitivity to ceftazidime and ciprofloxacin was observed in 55.3% and 48.7%, respectively.

More recently, Jindal et al. evaluated the antimicrobial susceptibility of isolates on 581 patients with culture-proven post-traumatic endophthalmitis at L.V. Prasad Eye Institute, Hyderabad, from January 2006 to March 2013 [23]. Comparing with the earlier published report from the same institute [17], they found that the susceptibility of gram-positive organisms continues to be highest to vancomycin; the susceptibility of CoNS to ciprofloxacin had reduced from 100% in 1999 to 77.3% in 2013.

A comparative analysis of all these studies is shown in Table 27.2.

The rates of resistance of gram-positives to antimicrobials (L.V. Prasad Eye Institute from India) over a 10-year period (January 2005 to December 2015) are shown in Fig. 27.3.

Gram-Negative Bacteria

Global Perspective

In the EVS, of the 19 gram-negative isolates tested for antibiotic susceptibility, the frequencies of susceptible isolates were amikacin, 89.5%; ceftazidime, 89.5%; and ciprofloxacin, 94.7% [8]. While 17/19 isolates were susceptible to both amikacin and ceftazidime, 2/19 were resistant to both. Additionally, one gram-negative isolate was resistant to only ceftazidime, and another isolate was resistant to only ciprofloxacin, but the later isolate was susceptible to both amikacin and ceftazidime.

Table 27.2 Antibiotic susceptibility profile of gram- positive bacteria isolated from endophthalmitis as reported in literature

Sl	Author et al. (year)	Study period	Location	Overall antibiotic susceptibility (%)						
				Vancomycin	Gentamicin	Ciprofloxacin	Gatifloxacin	Moxifloxacin	Amikacin	Cefazolin
1	Davis et al. [7]	1973–1986	USA	100	59	NA	NA	NA	NA	NA
2	Han et al. [8]	1990–1994	USA	100	NA	75.3	NA	NA	77	NA
3	Benz et al. [9]	1996–2001	USA	100	78.4	68.3	NA	NA	NA	NA
4	Recchia et al. [10]	1989–2000	USA	95	NA	67.2	NA	NA	NA	67.2
5	Gentile et al. [11]	1987–2011	USA	99.7	74.8	71	78	75.3	NA	48
6	Melo et al. [12]	2006–2009	Brazil	100	78.3	54	86	92	90.2	NA
7	Bispo et al. [13]	2000–2005	Brazil	100	NA	89.6	100	100	NA	NA
8	Falvarjani et al. [14]	2005–2015	Iran	100	NA	90	NA	NA	NA	NA
9	Long et al. [15]	1990–2009	China	NA	100	100	NA	NA	NA	NA
10	Liu et al. [16]	2004–2014	China	97.6	78.7	73.7	NA	NA	NA	12.7
11	Kunimoto et al. [17]	1991–1997	India	100	NA	50	NA	NA	100	75
12	Kunimoto et al. [18]	1989–2000	India	86	84.5	95	NA	NA	89	87
13	Anand et al. [19]	1995–1998	India	100	77.3	88.4	NA	NA	NA	92.6
14	Ramakrishnan et al. [21]	1997–2006	India	92	61	95.5	97.2	100	65.5	91.3
15	Bhatacharjee et al. [22]	2003–2013	India	100	NA	48.7	NA	NA	NA	54.5
16	Jindal et al. [23]	2006–2013	India	94.4	78.3	78.1	91	85	66	88

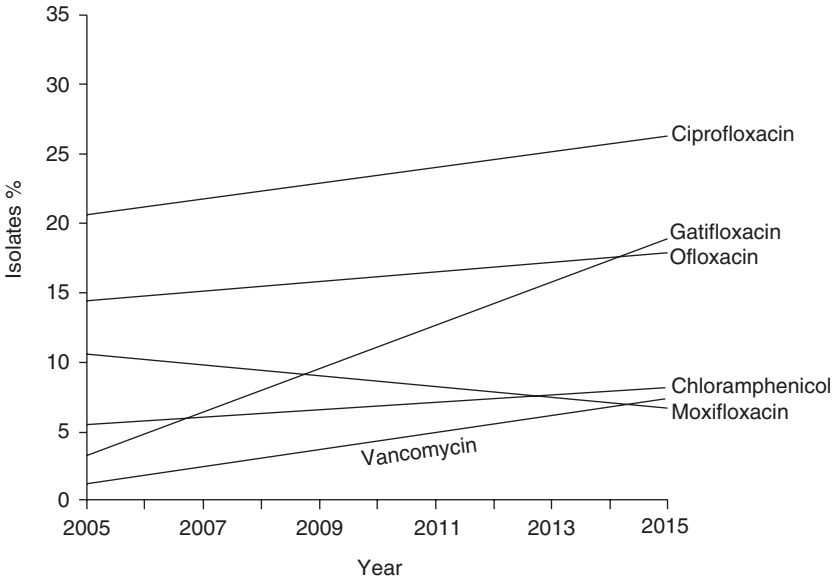

Fig. 27.3 Trends of antibiotic resistance by gram-positive organisms, 2005–2015 of all culture-proven endophthalmitis seen at the L.V. Prasad Eye Institute, Hyderabad (unpublished data)

Benz et al. have reported that among the gram-negative organisms, the sensitivities were the following: ciprofloxacin 94.2%, ceftazidime 80%, amikacin 81%, and gentamicin 75% [9]. Recchia et al. showed that all 15 tested gram-negative bacteria were completely sensitive to ceftazidime; but it could not be said for the aminoglycoside antibiotics (gentamicin, tobramycin, and amikacin) [10]. A higher percentage of gram-negative isolates in this study was additionally susceptible to gatifloxacin (95%, 19/20) and moxifloxacin (100%).

Gentile and co-workers reviewed the culture-positive endophthalmitis collected from 1987 to 2011 at the New York Eye and Ear Infirmary and found that among the gram-negative isolates, susceptibility to ceftazidime (91.5%) was statistically similar to that of ciprofloxacin (94.4%), amikacin (92.9%), gentamicin (92.8%), and imipenem (93.8%) [11]. This was in contrast to Benz et al. who reported that the susceptibility of gram-negative isolates for ciprofloxacin (94.2%) was greater than for ceftazidime (80.0%) [9].

Among the cases of post-traumatic endophthalmitis patients treated at Zhongshan Ophthalmic Center, Guangzhou, China, from 1990 to 2009, *P. aeruginosa* showed high levels of resistance compared to other bacteria, particularly to chloramphenicol (susceptibility to chloramphenicol was 33.3 and 16.7% in the first and second decade of study, respectively) [15]. In this study, *P. aeruginosa* was susceptible to ciprofloxacin, cefoperazone, cefuroxime, tobramycin, and ceftazidime (susceptibility range, 75%–83.3%) during the second decade. *B. proteus* showed 80%

susceptibility to both cefuroxime and ceftazidime, while there was a significant decrease in susceptibility to tobramycin (from 66.7 to 30%) and to neomycin (from 50 to 30%) between the two decades. *E. coli* was susceptible to both cefuroxime and ceftazidime (93.3%), but its susceptibility to ciprofloxacin and tobramycin decreased by 20% (from 100% to 80%) and by 34.2% (from 87.5% to 53.3%), respectively, between the two decades. Overall, ciprofloxacin showed the highest activity against all bacterial causes of post-endophthalmitis during the first decade, and ceftazidime showed the highest activity during the second decade [15].

Similarly at a referral center in Tehran, antibiotic resistance among the 28 gram-negative organisms was observed for ampicillin (71.2%; $n = 20$), cefazolin (50%; $n = 14$); ceftriaxone (28.5%; $n = 8$); gentamicin (17.8%; $n = 5$); ceftazidime, ciprofloxacin, and imipenem (10.7%; $n = 3$); and amikacin and ciprofloxacin (7.14%; $n = 2$). It was also noted that the ceftazidime-resistant isolates were sensitive to amikacin, and the amikacin-resistant isolates were sensitive to ceftazidime and ciprofloxacin [14].

Indian Perspective

Anand et al. (Chennai, South India) have reported that while all gram-negative bacteria were resistant to vancomycin, 55.5% were sensitive to gentamicin, 65.2% to cefotaxime, 68.1% to amikacin, 73.2% to ciprofloxacin, and 62.5% to ceftazidime [19]. Studies by Kunimoto and coworkers (Hyderabad, South India) [17, 18] have reported that between 1991 and 1997, the gram-negative organisms isolated from the post-traumatic endophthalmitis were most susceptible to ciprofloxacin (100%), and there was poor susceptibility to ceftazidime (66.7%); the gram-negative organisms isolated from postoperative endophthalmitis were susceptible to ciprofloxacin (87.5%) and amikacin (82.1%) and were poorly susceptible to ceftazidime (60.9%). Similar studies on culture-proven endophthalmitis treated at Tirunelveli, South India, from 1997 to 2006 showed that gram-negative bacilli were susceptible to gatifloxacin (100%), amikacin (100%), ciprofloxacin (97.4%), and ofloxacin (97.4%) [21]. In contrast, Bhattacharjee et al. (Guwahati, Northeast India) showed that 45.5% of the isolates were sensitive to amikacin, 33.3% to cefotaxime, 55.3% to ceftazidime, and 48.7% to ciprofloxacin [22].

Recent series by Jindal et al. (Hyderabad, South India) showed that gram-negative bacteria from post-traumatic endophthalmitis were generally susceptible to gatifloxacin (92.9%), ofloxacin (89.4%), chloramphenicol (88.6%), ciprofloxacin (86.6%), amikacin (83.5%), and ceftazidime (77.2%) [23]. They also reported that in a setting of delayed post-cataract surgery endophthalmitis, between 2006 and 2013, the gram-negative isolates were most susceptible to ofloxacin (85.7%); ceftazidime, ciprofloxacin, gatifloxacin, and moxifloxacin (71.4% each); and amikacin (57.1%) [24]. Ramakrishnan et al. reported a comparable antimicrobial susceptibility of the organisms in both acute post-cataract and post-traumatic endophthalmitis in the same geographic region [21].

A comparative analysis of all these studies is shown in Table 27.3.

The rates of resistance of gram-negatives to antimicrobials (L.V. Prasad Eye Institute from India) over a 10-year period (January 2005–December 2015) are shown in Fig. 27.4.

Anaerobic Bacteria

There is little information on the patterns of anaerobic infection in the eye. The oxygen of the central vitreous cavity is very low, and hence anaerobic bacteria might therefore be expected to cause endophthalmitis if introduced in sufficient numbers into the vitreous cavity during intraocular surgery or trauma. While Jones and Robinson have reported ten cases of anaerobic endophthalmitis in 1977 [25], most recent endophthalmitis series have not reported any, possibly because they have not used optimal anaerobic microbiologic techniques. Ormerod et al. reported anaerobic bacteria susceptibility from a 5-year period (1981–1985) at the Massachusetts Eye and Ear Infirmary, Boston, USA [26]. In this study *P. acnes* was most susceptible to penicillin, cefoxitin, cefotaxime, clindamycin, chloramphenicol, and imipenem, and

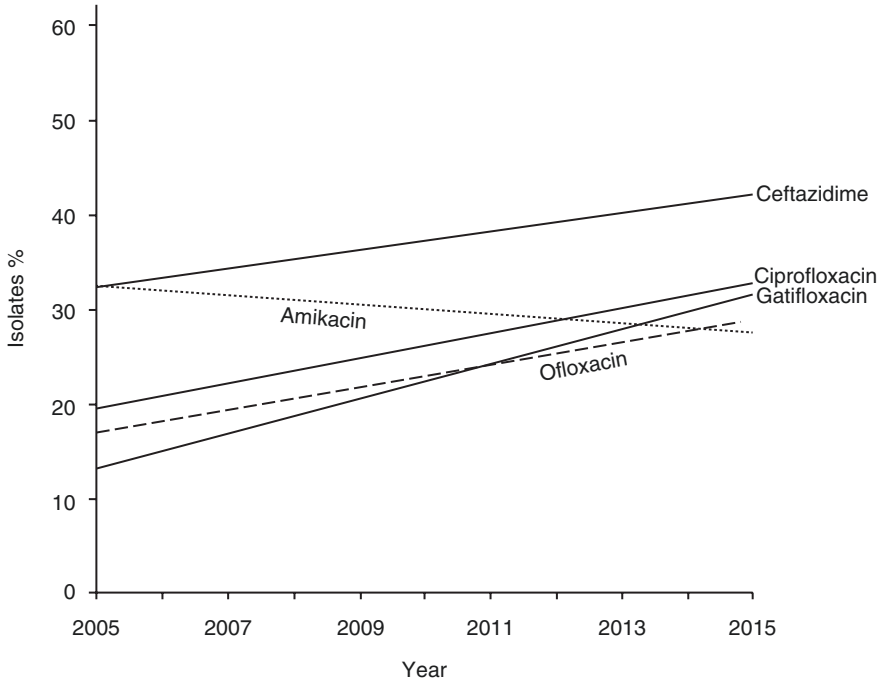

Fig. 27.4 Trends of antibiotic resistance by gram-negative organisms from 2005–2015 of all culture-proven endophthalmitis seen at the L.V. Prasad Eye Institute, Hyderabad, India (unpublished data)

Table 27.3 Antibiotic susceptibility profile of gram-negative bacteria isolated from endophthalmitis as reported in literature

Sl	Author et al. (year)	Study period	Location	Overall antibiotic susceptibility (%)						
				Vancomycin	Gentamicin	Ciprofloxacin	Gatifloxacin	Moxifloxacin	Amikacin	Ceftazidime
1	Han et al. [8]	1990–1994	USA (EVS)	0	NA	94.7	NA	NA	89	89.5
2	Benz et al. [9]	1996–2001	USA	NA	70	94.2	NA	NA	80.9	80
3	Recchia et al. [10]	1989–2000	USA	67	NA	NA	NA	NA	NA	100
4	Gentile et al. [11]	1987–2011	USA	NA	92.8	94.4	95	100	92.9	91.5
5	Bispo et al. [13]	200–2005	Brazil	NA	80.6	96.7	100	100	87.1	85
6	Falvarjani et al. [14]	2005–2015	Iran	NA	76.5	100	NA	NA	88.3	83.4
7	Anand et al. [19]	1995–1998	India	0	55.5	73.2	NA	NA	68.1	62.5
8	Kunimoto et al. [18]	1991–1997	India	76.2	91.7	100	NA	NA	95.2	66.7
9	Kunimoto et al. [17]	1989–2000	India	NA	100	NA	NA	NA	NA	100
10	Ramakrishnan et al. [21]	1997–2006	India	7.8	89.6	97.4	100	25	96.1	76.6
11	Bhatacharjee et al. [22]	2003–2013	India	NA	NA	48.7	NA	NA	45.5	55.3
12	Jindal et al. [23]	2006–2013	India	0	56.2	64	70.8	50	67.4	57.3
13	Jindal et al. [24]	2006–2013	India	71.4	NA	71.4	71.4	71.4	57.1	71.4

most anaerobes, including *P. acnes*, were resistant to gentamicin, cefazolin, and vancomycin. Later, Hall et al. reported that six *P. acnes* isolates from patients with chronic infectious endophthalmitis were most susceptible to vancomycin, penicillin, and cefazolin [27].

Emanuelli et al. reviewed all anaerobic bacterial vitreous isolates between January 1991 and September 2011 at the Bascom Palmer Eye Institute, Miami, USA, [28] and found that 92% of the isolates were sensitive to vancomycin (222 and 22 μg/mL), 66.7% were sensitive to high-dose ceftazidime (5 μg/mL), and 33.3% were sensitive to low-dose ceftazidime (0.5 μg/mL). While 41.7% of the isolates were sensitive to high-dose moxifloxacin (1.1 mg/mL), 25% were sensitive to low-dose moxifloxacin (0.11 mg/mL), 50% of the isolates were sensitive to high-dose gatifloxacin (0.67 mg/mL), and 8.3% were sensitive to low-dose gatifloxacin (0.07 mg/mL). Vancomycin was the most effective antibiotic against anaerobes pathogens. The fluoroquinolones had a variable effect in the high-dose group but were not generally effective in the low-dose group.

Challenges and Dilemmas: Increasing Resistance to Common Antibiotics

As described in the earlier sections, endophthalmitis may also be caused by organisms that are resistant or have reduced susceptibility to standard antimicrobial regimens.

Miller et al. showed that the newer fluoroquinolones, gatifloxacin and moxifloxacin, demonstrated an in vitro efficacy of less than 80% for coagulase-negative staphylococci endophthalmitis in their study [29]. They hypothesized that ciprofloxacin resistance may serve as a surrogate for concurrent in vitro resistance for gatifloxacin and moxifloxacin, and this resistance had increased significantly since year 2000. This increasing resistance over the decades to various antimicrobials is a concern as they may have important implications for the prevention and treatment of endophthalmitis.

The following sections will focus on such challenges in endophthalmitis.

Methicillin-Resistant *S. aureus* (MRSA) and *S. epidermidis* (MRSE)

The issue of potential infection by MRSA and MRSE is gaining attention as more of these resistant strains appear in endophthalmitis isolates around the world. In 2010, Major et al. from the Bascom Palmer Eye Institute, Miami, USA, reported that MRSA was recovered in 41% of 32 cases of endophthalmitis caused by *S aureus* in a retrospective series from 1995 through 2008 [30]. Weber et al. identified the exposure to fluoroquinolones as a risk for MRSA infection in hospitalized patients [31], this was postulated due to changes in adhesion and favored colonization. Gentile et al. also found a statistically significant increase in both *S. aureus* and *S.*

epidermidis isolates resistant to methicillin/oxacillin in their 25-year review of culture-positive endophthalmitis, collected from 1987 to 2011 at the New York Eye and Ear Infirmary, USA [11]. During that study, S. *aureus* and *S. epidermidis* methicillin resistance rates increased from 18% to 31%, respectively, to more than 50% in each case. There was no methicillin resistance to staphylococcal species, other than *S. aureus* and *S. epidermidis* though there was no significant change in methicillin resistance over the same time period; all of them were sensitive to vancomycin.

Vancomycin-Resistant Gram-Positive Bacteria Including Vancomycin-Resistant *S. aureus* (VRSA)/Vancomycin-Resistant *Enterococci* (VRE)

Relhan et al. evaluated all published reports of endophthalmitis caused by gram-positive organisms with reduced vancomycin susceptibility and/or vancomycin resistance, from 1990 to 2015 [32]. In their series, 9 were multidrug resistant including fluoroquinolones ($n = 5$), penicillins ($n = 5$), cephalosporins ($n = 3$), and aminoglycosides ($n = 2$). *Leuconostoc* species, well-known opportunistic infectious agents with intrinsic resistance to vancomycin, were reported in 3 of 27 cases [32–35]. They suggested alternative antibiotics in face of vancomycin-resistant organisms; these antibiotics included systemic or intravitreal linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline. They also included a series by Kurien et al. [36] which reported 3 cases caused by *Streptococcus* species (3/27) with reduced vancomycin susceptibility, and all these 3 patients underwent enucleation/evisceration. In 2007, two postoperative endophthalmitis cases were additionally reported with vancomycin-resistant *Enterococcus* species [37, 38]. In 2011, endophthalmitis caused by vancomycin-resistant *Staphylococcus* species was reported for the first time [39, 40]. Gentile et al. have reported a single case of vancomycin-resistant *Enterococcus* (VRE) endophthalmitis in their series which was susceptible to ceftriaxone, cefuroxime, imipenem, and penicillin G [11]. The vancomycin-resistant *Nocardia exalbida*, also resistant to ciprofloxacin, in that series was susceptible to trimethoprim sulfamethoxazole, amikacin, and ceftriaxone.

Multidrug-Resistant (MDR) Isolates

Multidrug resistance is defined as resistance to two or more different groups of typically susceptible classes of antibiotics. Because MDR is emerging as a major problem in the management of other systemic and ocular infections, it is important to recognize such pathogens early. Long et al. observed multidrug resistance in several gram-negative organisms (*P. aeruginosa*, *B. proteus*, *and E. coli*) to all the tested antibiotics, especially to gentamicin, neomycin, chloramphenicol, and ofloxacin [15]. Pathengay et al., in a review of records of culture-proven bacterial

endophthalmitis between 2000 and 2007, focused on MDR in bacteria-causing endophthalmitis at the L.V. Prasad Eye Institute, South India [41]. They reported the MDR was more common in gram-negative bacteria (n = 33/210; 15.7%) compared to gram-positive bacteria (n = 9/555; 1.6%). Fifteen (45%) of the 33 gram-negative isolates were resistant to ceftazidime, 18 (54.5%) were resistant to amikacin, and 11 (33.3%) were resistant to both amikacin and ceftazidime. Five (55.56%) of the 9 gram-positive isolates were resistant to vancomycin. Later Jindal et al. evaluated 12 acute-onset postoperative gram-negative bacterial endophthalmitis cases resistant to both ceftazidime and amikacin seen between 2005 and 2010 at the L.V. Prasad Eye Institute, South India [42] and found that 5 were susceptible to all fluoroquinolones while 6 were susceptible to imipenem. In total, 11 of 12 isolates were susceptible to either of these two drugs. Only one *Pseudomonas* isolate was resistant to all tested antimicrobials. This was further corroborated by Sanghi et al. at the L.V. Prasad Eye Institute who reviewed the treatment of multidrug-resistant *Klebsiella*-related postoperative endophthalmitis in three patients seen between 2013 and 2014 [43] and found that all isolates were sensitive to imipenem. Additionally, one isolate was also found to be sensitive to ceftazidime and colistin.

Antifungal Susceptibility Profile

There are very few agents available for the treatment of fungal endophthalmitis. The inability to routine testing of the sensitivity of the fungal pathogens under laboratory conditions presents a challenge in deciding the treatment. The development of resistance in fungal pathogens and concerns of focal retinal necrosis might occur with low doses of amphotericin B which have prompted testing of new antifungal alternatives. Aydin et al. reported a case of an72-year-old male with postoperative endophthalmitis caused by *Scopulariopsis* species; the in vitro susceptibility to amphotericin B, voriconazole, and caspofungin was >32 μg/mL, 8 μg/mL, and 4 μg/mL, respectively [44]. In a series of culture-proven fungal endophthalmitis seen at the University of Miami (n = 151) between January 1990 and June 2010, the median MICs for amphotericin B, fluconazole, and voriconazole were 1 μg/mL (range, 0.125–16 μg/mL), 64 μg/mL (range, 0.125–64 μg/mL), and 0.25 μg/mL (range, 0.015–8 μg/mL), respectively [45]. All *Candida* isolates in this study were susceptible to intravitreal amphotericin B and oral fluconazole, while all *Aspergillus* isolates were resistant to oral fluconazole and intravitreal amphotericin B, but sensitive to voriconazole. All 14 *Fusarium* cases were resistant to intravenous amphotericin B and oral fluconazole; however 9 of 14 (64.3%) *Fusarium* were sensitive to intravitreal amphotericin B [45].

The MICs of the drugs against *Candida* species isolated from patients with endophthalmitis between September 2010 and March 2014 studied at the L.V. Prasad Eye Institute, Hyderabad, South India [46], are elaborated in Table 27.4. The study found that 11of 12 isolates were susceptible to amphotericin B, 6/12 isolates were susceptible to voriconazole, and all of them were sensitive to natamycin. The resistance or susceptibility to itraconazole was dose dependent. Resistance to voriconazole, caspofungin, and fluconazole was seen in 2 (15.3%), 3 (23%), and 5 (38.4%) isolates, respectively.

Table 27.4 Antifungal susceptibility profile of various *Candida* isolates from endophthalmitis, extracted from the study by Motukupally et al. [46]

Organism (n)	MIC range in μg/mL (susceptibility %)[a]					
	AB	IT	VO	CS	FL	NA
C. albicans (4)	0.047–0.25 (100)	0.25–2 (0)	0.064–>32 (75)	0.032–>32 (50)	1.5–3 (75)	0.25–8 (100)
C. glabrata (1)	0.25 (100)	>32 (0)	1.0 (0)	0.38 (0)	1.5 (100)	0.25 (100)
C. tropicalis (1)	1.0 (100)	0.75 (0)	0.25 (0)	0.094 (100)	4.0 (0)	0.5 (100)
C. pelliculosa (1)	0.094 (100)	0.75 (0)	0.094 (100)	0.032 (100)	1.50 (100)	1.0 (100)
C. utilis (1)	0.125 (100)	>32 (0)	0.032 (100)	0.064 (100)	1.0 (100)	2.0 (100)
C. parapsilosis (1)	0.19 (100)	0.25 (0)	0.094 (100)	0.38 (100)	12 (0)	8.0 (100)
C. famata (1)	>32 (0)	16 (0)	0.38 (0)	>32 (0)	64 (0)	4.0 (100)
Candida species (2)	0.094–0.125 (100)	1.0–8.0 (0)	0.25–0.75 (0)	0.19–0.38 (50)	12–128 (0)	2.0 (100)

[a]Intermediate results are considered as resistant

Conclusion

Monitoring the causative organisms of endophthalmitis and their resistance is important in detecting trends to guide changes in the empiric management of endophthalmitis or reaffirm current practices. Vancomycin retains excellent activity against nearly all gram-positive organisms implicated in endophthalmitis, but the choice of gram-negative coverage needs a careful tailoring to the local data. Current microbiologic investigation of endophthalmitis almost certainly underestimates the role of anaerobic bacteria, particularly in mixed infections. The inclusion of antifungal therapy should be strongly considered if local data suggest a high prevalence of fungal infection or in cases of traumatic endophthalmitis, particularly in the Indian subcontinent. In addition, from a global epidemiological standpoint, the current findings of emerging resistance should remind physicians to be judicious in their use of antibiotics in any patient, bearing in mind that indiscriminate use may potentially contribute to the undesirable consequence of increased resistance.

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Part V
Science of Endophthalmitis Treatment: Pathology

Chapter 28
Pathology of Endophthalmitis

Ranju Kharel (Sitaula), Chanchal Poddar, and Jyotirmay Biswas

Endophthalmitis is a serious intraocular inflammatory disorder affecting the vitreous cavity that can result from exogenous or endogenous spread of infecting organisms into the eye [1]. It may be categorized by clinical course (acute versus chronic), by etiology (infectious versus noninfectious), by the route of entry of the causative agent (exogenous versus endogenous), and by the organism(s) causing the infection (bacteria, fungi, parasites, and, rarely, viruses). Certain organisms tend to be associated with particular clinical settings, means of intraocular access, and types of inflammation (acute, chronic non-granulomatous, chronic granulomatous, or mixed cellular response) [2].

Pathogenesis

In endophthalmitis, inflammation originates from infection of the vitreous cavity. But the specific pathogenesis of the cellular damage due to excessive immune response is still not exactly understood. Cytokines, the intercellular messengers, play an important role in mediating processes of inflammation and repair [3]. The endophthalmitis immune response generates cell activation and cytokine secretion to suppress the infectious process [3]. Other mediators such as Toll-like receptors, high-mobility group box 1 proteins, aB-crystallin, and apoptosis have been studied

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during clinical and experimental cases of endophthalmitis [3]. The factors responsible for cellular necrosis and tissue damage in endophthalmitis depend on the load, the virulence, and the toxin production by the microorganism. The production of different types of bacterial enzymes such as hemolysins, lipases, enterotoxins, proteases, collagenases, and hyaluronidases damages the host tissue [3]. In endophthalmitis, breech in the blood–ocular barrier and immune-privileged microenvironment of the eye predisposes to the destruction of anatomical and functional integrity of delicate ocular tissues; also the retinal cell apoptosis is increased [4]. High-mobility group box 1 (HMGB1) proteins are another class of molecules that have been identified in high concentrations in endophthalmitis [5].

Types/Classification

Exogenous endophthalmitis refers to infections resulting from breach of the globe exterior through surgery or trauma or by fulminate progression of inflammatory processes such as keratitis or scleritis [2, 3]. It can be further divided into:

Postsurgical endophthalmitis—It is a complication of intraocular surgeries like cataract surgery, corneal surgeries (penetrating keratoplasty, keratoprosthesis insertion, refractive corneal surgeries), vitreous procedures (intravitreal injections, vitrectomies), glaucoma filtration surgery (blebs, glaucoma valve placements), retinal surgery, and even strabismus correction [2]. It can be further classified as "acute-onset" (within 6 weeks), "delayed-onset" (more than 6 weeks), and "glaucoma filtering surgery-associated" endophthalmitis [6]. The common associated organisms are listed in Table 28.1.

Post-traumatic endophthalmitis—Acute or delayed onset endophthalmitis is an important complication of open globe injury, and these are more often associated with a poorer visual outcome [7].

Endogenous (metastatic) endophthalmitis—It is a condition where the infectious agent travels via bloodstream and multiplies in the choroid, eventually infiltrating the retina and spreading at the vitreous [8].

Table 28.1 Common microorganisms associated with endophthalmitis

Endophthalmitis	Acute onset	Delayed onset	Glaucoma filtration surgery
Common microorganisms	Coagulase negative Staphylococci	*Propionibacterium acnes*	*Haemophilus influenzae*
	Staphylococcus aureus	Coagulase negative Staphylococci	*Staphylococcus* species
	Gram-negative bacteria	Fungi	

Specimen for Study of Pathology of Endophthalmitis

1. Aqueous
2. Vitreous
3. Lens capsule/intraocular lens (IOL)
4. Eviscerated tissue
5. Enucleated eyeball

Pathology of Involved Tissue in Endophthalmitis

The primary site of involvement is vitreous; retina and choroid show inflammatory cell deposit due to release of inflammatory mediators and autolytic enzymes from leukocytes. The predominant cell type in acute inflammation is the polymorphonuclear leukocyte; it is lymphocyte (*white arrow*) and the plasma cell in chronic inflammation. These cells are commonly seen in hematoxylin and eosin (H&E) (Fig. 28.1).

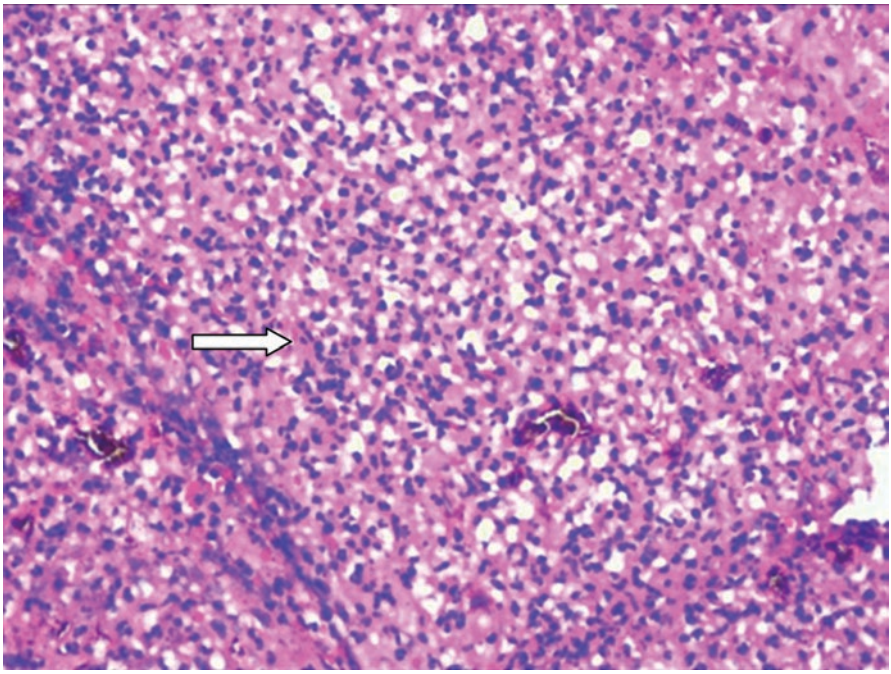

Fig. 28.1 Photomicrograph showing polymorphonuclear leukocyte and lymphocytic infiltration in eviscerated tissue of endophthalmitis (H&E ×100)

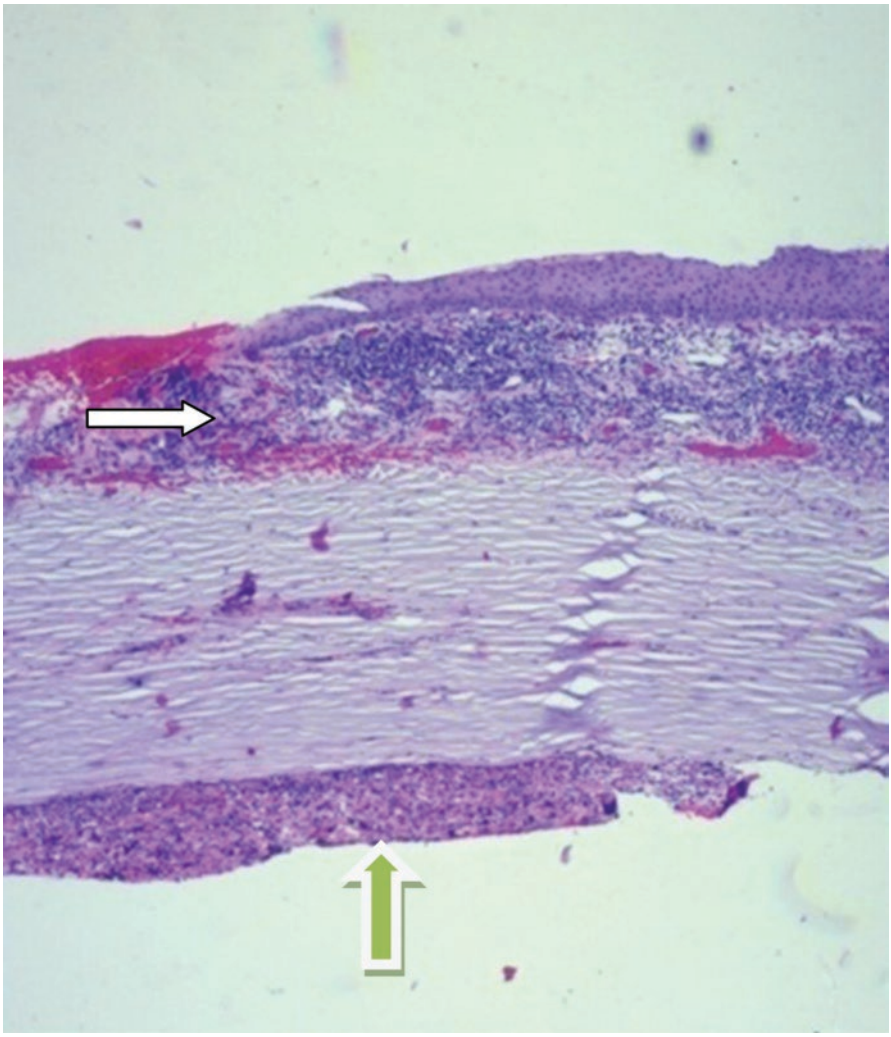

Fig. 28.2 Photomicrograph showing dense polymorphonuclear infiltration in all layers of cornea with areas of hemorrhage in corneal tissue (*white arrow*) along with plastered exudates behind the endothelium of cornea and in anterior chamber (*green arrow*) (H&E ×40)

Pathology of Cornea

The cellular migration into the anterior chamber may plaster in the endothelial surface and later may invade the corneal tissue (Fig. 28.2). Disorganization and edematous stoma may be visible if associated with raised intraocular pressure. A marked polymorphonuclear migration into cornea with corneal ring abscess formation in response to the bacterial invasion or locally produced inflammatory mediators is hallmark of *Bacillus cereus* [9]. Besides, hyphae of fungus may also be observed within the corneal stroma in case of fungal endophthalmitis.

Pathology of Anterior Chamber

Exudation of polymorphonuclear leukocytes with or without macrophage is seen in aqueous humor. The rupture of anterior vitreous face with disruption of blood–aqueous barrier is the cause of exudates in anterior chamber (Fig. 28.2). Sometimes, there can be necrotic leukocytes admixed with a large amount of uveal pigment leading to brown hypopyon due to *Streptococcus bovis* endogenous endophthalmitis [10].

Pathology of Lens

Clustering of microorganisms like *Pseudomonas aeruginosa* and *Paecilomyces lilacinus* may occur within the lens capsule following accidental trauma causing the rupture of capsule or after the cataract surgery creating a localized infection within the lens capsular sac [9]. Sometimes, residual lens cortex, phacotoxic reaction, and phacoanaphylaxis reaction can lead to sterile granulomatous endophthalmitis [11]. It is characterized histologically by a zonal granulomatous inflammatory reaction to the lens capsular remnants with central polymorphonuclear reaction.

Pathology of Uveal Tract

The choroidal inflammation may be non-granulomatous or granulomatous with or without necrosis (Fig. 28.3).

Dense infiltrates of choroid with foamy macrophages are seen in endophthalmitis due to tuberculosis. In fungal endophthalmitis, granulomatous inflammation with necrotizing chorioretinitis can be present, and the fungal hyphae may be visible in choroidal layer.

The adjacent iris and ciliary body may show an infiltration of plasma cells and lymphocytes.

Pathology of Vitreous

Vitreous is the prime site of involvement. It becomes infiltrated with purulent exudates. These exudates release inflammatory mediators that are responsible for the disruption of the integrity of blood–ocular barrier. The leukocytic infiltration of the vitreous causes liquefaction of the vitreous leading to posterior vitreous detachment and retinal detachment. Multiple vitreous microabscesses are a characteristic finding in fungal endophthalmitis where the fungal hyphae are surrounded by macrophages and lymphocytes (Fig. 28.4) [12].

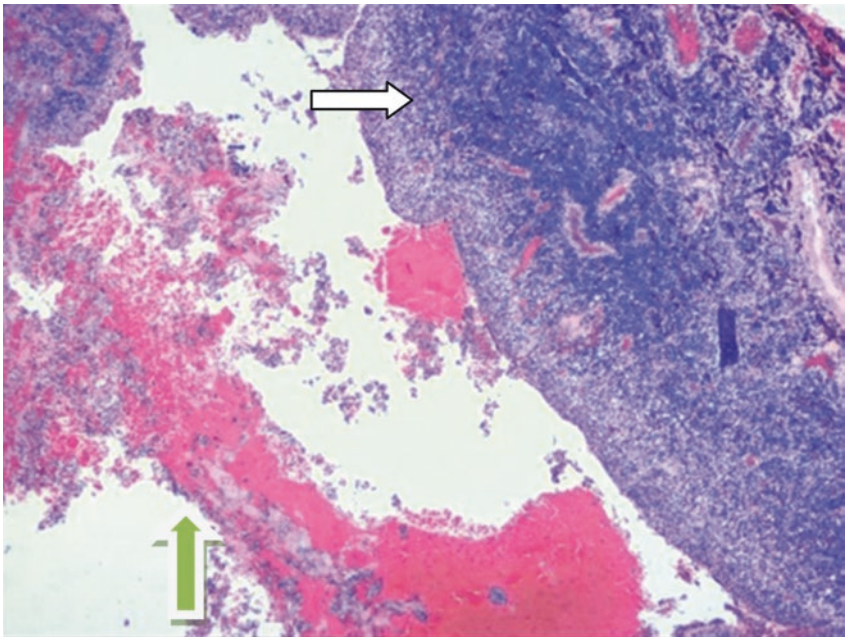

Fig. 28.3 Photomicrograph showing dense lymphocytic infiltration of choroid (*white arrow*) with hemorrhagic areas in vitreous (*green arrow*) in a case of acute endophthalmitis (H&E ×100)

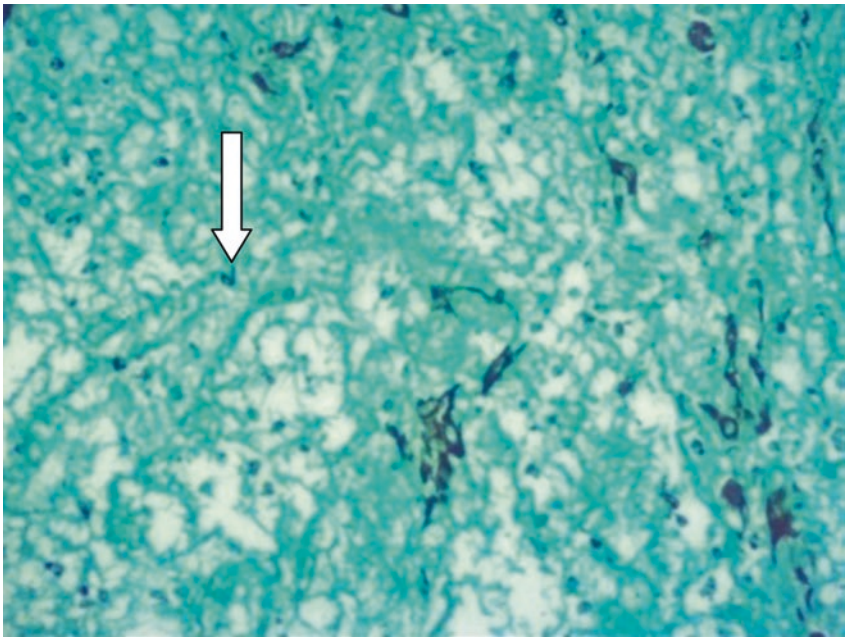

Fig. 28.4 Grocott's methenamine silver (GMS) stain showing septate hyphae of fungus (*white arrow*) in vitreous ×400

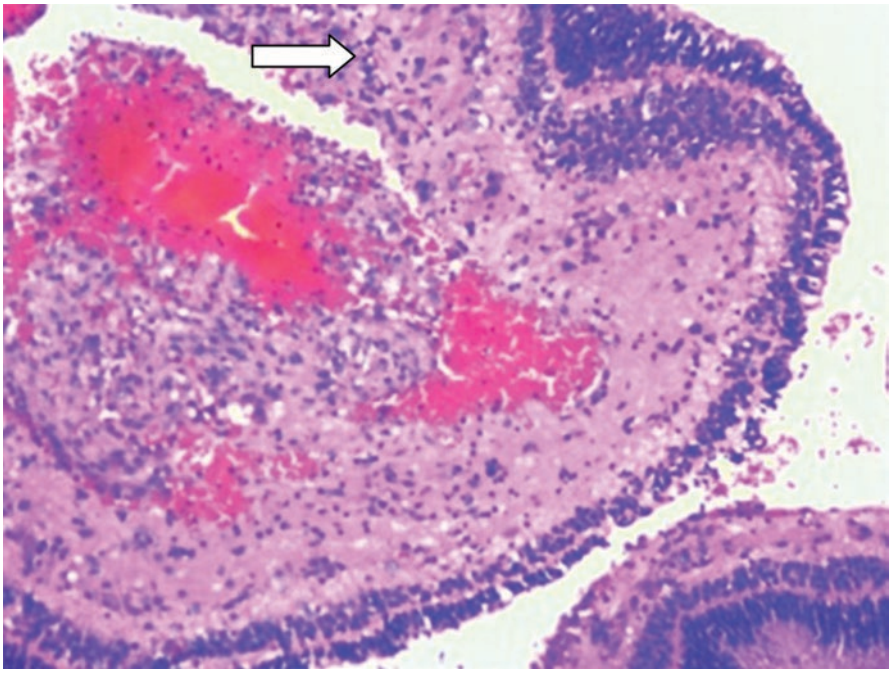

Fig. 28.5 Photomicrograph showing the dense inflammatory cellular infiltration in the retina and adjoining vitreous involvement with areas of hemorrhage (*white arrow*) (H&E ×100)

Pathology of Retina

The retina is characterized by infiltration of acute (polymorphonuclear leukocytes) or chronic (lymphocytes and plasma cells) inflammatory cells. The toxins, inflammatory mediators, and autolytic enzymes released from the leukocytes result in retinal necrosis with intraretinal hemorrhage (Fig. 28.5). The exudation of proteinaceous nature could lead to exudative retinal detachment, and the retinal ischemia with preretinal fibrovascular membrane that could lead to tractional retinal detachment.

The disruption in the retinal tissue integrity, exudation around vessels, or pigment accumulation around retinal vessels can also be observed. The endophthalmitis due to organism like *Treponema pallidum* and fungi can produce necrotizing retinitis with granulomatous inflammation. Fungal hyphae may be seen in cut section of retina with or without spreading up to the surface of Bruch's membrane [12]. Rao et al. have documented the histopathological difference between fungal endophthalmitis by *Aspergillus* and *Candida*. *Aspergillus* grows preferentially along the subretinal pigment epithelium and subretinal space, but *Candida* does not [13].

Pathology of Optic Nerve

Cellular infiltration advancement from vitreous or retina to the optic nerve can be visible in histopathology.

Treatment of Endophthalmitis

Microbial endophthalmitis treatment is difficult. Restoration of functional and anatomical outcome is a challenging task due to disturbance in the delicate anatomy and physiology of ocular tissues. Inflammation-induced opacity of the cornea, anterior chamber, lens, and/or vitreous impedes formation of a clear image on the retina. Inflammation-mediated damage to the trabecular meshwork and/or ciliary body may produce blinding glaucoma or ocular hypotony [14]. Most critically, damage to the neurosensory retina and retinal pigment epithelium may destroy the basic photochemical process of vision.

Conclusion

Treatments available to neutralize the infection and to diminish the inflammatory damage are intravitreal antibiotics, intravitreal corticosteroids, and vitrectomy [3]. The availability of histopathological study of endophthalmitis allows better understanding of the pathogenesis of the disease. As seen in histopathological section, all intraocular tissues can be involved in this condition. Newer diagnostic tool like polymerase chain reaction (PCR) has greatly helped in the early diagnosis of different infective causes of endophthalmitis; this helps better management resulting in good prognosis of endophthalmitis. Finally, elimination of microorganisms, control of intraocular inflammation before the retinal tissue damage, and protection at cellular level are the core factors to achieve good prognosis in this devastating condition.

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Part VI
Prophylaxis and Prevention

Chapter 29
Endophthalmitis Prophylaxis: Different Practices from Around the World

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Endophthalmitis remains a serious and potentially blinding complication of all intraocular procedures. Visual outcomes vary widely, and the prognosis remains guarded even when treatment is started quickly and appropriately. Prophylaxis remains the most important strategy to decrease morbidity associated with this disease [1]. Practices that reduce the risk of endophthalmitis vary extensively between nations because of the limited data from randomized clinical trials (RCTs).

Povidone-iodine preparation prior to any surgical procedure in non-allergic patients is a worldwide-accepted strategy that reduces endophthalmitis incidence (Fig. 29.1) [2]. This is the only technique to achieve category II evidence. Mostly considered controversial, chlorhexidine is currently used in some centers in patients with iodine allergy. However, chlorhexidine is toxic to the corneal endothelium and chlorhexidine prophylaxis has not been validated for intraocular surgery.

Generally, the most likely causative organisms may be predicted based on the procedure (Table 29.1) [3–5]. For example, in the USA, the most common isolates from acute-onset postoperative endophthalmitis following cataract surgery are coagulase-negative staphylococci, whereas endophthalmitis following intravitreal injection is more commonly associated with more virulent organisms such as streptococci [4, 5]. Different isolates are more prevalent in different parts of the world. In addition, local standards of care vary widely, especially with respect to the use of prophylactic antibiotics.

The present chapter will discuss different prophylaxis techniques that are practiced around the world for cataract surgery and for intravitreal injections.

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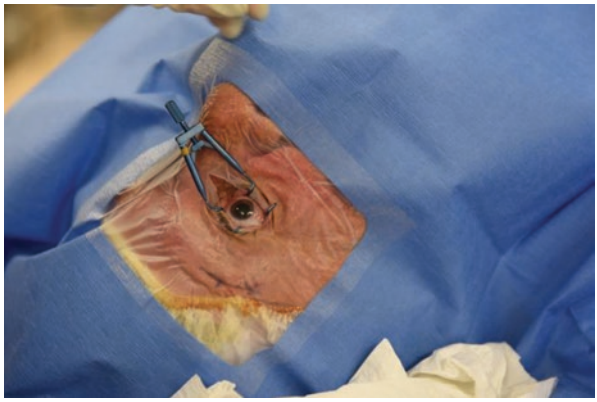

Fig. 29.1 Photograph demonstrating the "prep" for cataract surgery. Note the surgical drape, eyelid speculum, and evidence of povidone-iodine (Image courtesy of Guillermo Amescua, MD)

By definition, acute-onset postoperative endophthalmitis occurs within 6 weeks of the procedure, while delayed-onset (chronic) postoperative endophthalmitis occurs more than 6 weeks following the procedure.

Cataract Surgery

The incidence of endophthalmitis after cataract surgery may differ depending on multiple factors including patient demographics, surgeons, instruments, techniques, and unknown factors. Large series have reported rates of acute-onset postoperative endophthalmitis ranging from 0.03 to 0.2% [1, 6, 7]. Published data from the US Centers for Medicare and Medicaid in 2003–2004 estimated the rate at 0.1% [8]. During this timeframe, the vast majority of US centers did not use intracameral antibiotics. A contemporaneous study (2002–2004) performed in Sweden when most patients received intracameral antibiotics reported the rate at 0.048% [9]. A study using data from the American Academy of Ophthalmology's Intelligent Research in Sight (IRIS) Registry and US Centers for Medicare and Medicaid from 2010 to 2014 reported an incidence of endophthalmitis after cataract surgery of 0.14% [6].

The European Society of Cataract and Refractive Surgeons (ESCRS) designed a multicenter RCT to identify the risk factors and report on the incidence of postoperative endophthalmitis after cataract surgery [10]. The study included over 16,000 patients that were randomized to (1) no antibiotics, (2) postoperative topical levofloxacin, (3) intracameral cefuroxime, or (4) intracameral cefuroxime and postoperative topical levofloxacin. In this study, intracameral cefuroxime was associated with an approximate fivefold decrease in the rates of postoperative endophthalmitis. In addition, clear corneal incision surgery was associated with an approximate sixfold increased risk, and silicone intraocular lenses were associated with an approximate threefold increased risk.

Table 29.1 Common organisms associated with endophthalmitis

Acute-onset postoperative	Delayed-onset postoperative	Filtering bleb associated	Posttraumatic	Endogenous	Associated to microbial keratitis	Associated with intravitreal injection
Streptococcus spp.	*Propionibacterium acnes*	*Streptococcus* spp.	*Staphylococcus* spp.	*Candida albicans*	Gram-negative organisms	Coagulase-negative staphylococci
Coagulase-negative staphylococci spp.	*Candida parapsilosis*	*Haemophilus influenzae*	*Bacillus cereus*	*Aspergillus* spp.	*Staphylococcus aureus*	
Staphylococcus aureus	Coagulase-negative staphylococci				*Fusarium* spp.	

There are several important criticisms of this study. The relatively high rates of endophthalmitis in eyes not randomized to receive intracameral cefuroxime (approximately 0.2%) may have exaggerated the apparent benefit of these antibiotics. The study design allowed multiple different surgical techniques, which may have introduced bias [11]. The choice of levofloxacin as the postoperative topical antibiotic, rather than the more efficacious fourth-generation fluoroquinolones, might have influenced the results [12].

Despite these criticisms, following the publication of the ESCRS trial, the use of intracameral antibiotics became more common in many parts of the world. Multiple nonrandomized series, most of which were retrospective, were subsequently reported in the UK, Spain, France, Singapore, the USA, Sweden, Japan, Portugal, Ireland, Israel, and other nations (Table 29.2) [13–32].

When evaluating these results, it is important to consider that:

- Observational series represent a lower level of evidence than do RCTs. (The only RCT that specifically evaluated this topic was the ESCRS trial.) In many of these observational studies, two different groups of patients were compared: patients operated during an earlier timeframe (not receiving intracameral antibiotics) and different patients operated during a later timeframe (receiving intracameral antibiotics). Many factors other than the introduction of intracameral antibiotics may have impacted the reduced endophthalmitis rates, including advances in equipment, surgical techniques, topical antibiotics, and surgeon learning curves [12].
- Not all series reported a benefit associated with intracameral antibiotics. Two studies from Canada and India reported that intracameral antibiotics were not associated with a decreased rate of endophthalmitis (compared to a similar group of patients operated without intracameral antibiotics) [31, 32].
- In many of these series, the rates of endophthalmitis in patients operated without intracameral antibiotics were relatively high, in the range of 0.2% (similar to the rates of patients in the ESCRS study not randomized to receive intracameral cefuroxime) [10, 30]. In contrast, other series have reported very low rates of endophthalmitis without the use of intracameral antibiotics (approximately 0.06%) [33, 34], which are similar to the rates reported in many other series with the use of intracameral antibiotics.

Intracameral antibiotics may be associated with dilution errors, cystoid macular edema, toxic anterior segment syndrome (TASS), and selection of resistant organisms [35]. Intracameral vancomycin is reported to be associated with hemorrhagic occlusive retinal vasculitis and severe visual loss [36]. Intracameral aminoglycosides are associated with retinal vascular toxicity and severe visual loss [37]. Intracameral antibiotics are associated with fungal infections: in one report, seven consecutive patients developed endophthalmitis caused by *Fusarium* species following the use of intracameral cefuroxime [38].

Aprokam (Thea Pharmaceuticals, Clermont-Ferrand, France), a prepackaged formulation of cefuroxime for intracameral use, is approved by the European Medicines Agency for cataract surgery. This formulation of cefuroxime decreases concerns about compounding. However, this agent is not available in many nations,

Table 29.2 Selected reports of endophthalmitis with intracameral antibiotics after cataract surgery [13–32]

Series	*n*	Nation	Intracameral antibiotics	Rate without intracameral antibiotics (%)	Rate with intracameral antibiotics (%)	*p*-value
ESCRS [10]	16,603	Multiple	Cefuroxime	0.18–0.23	0.025–0.050	0.005
Daiven et al. [13]	3,351,401	France	Cefuroxime	0.11	0.05	0.001
Yu-Wai-Man et al. [14]	36,743	UK	Cefuroxime	0.14	0.046	0.0068
Garat et al. [15]	18,579	Spain	Cefazolin	0.39	0.032	<0.0000001
Romero-Aroca et al. [16]	25,001	Spain	Cefazolin	0.63	0.05	<0.001
Rodriguez-Caravaca et al. [17]	19,463	Spain	Cefuroxime	0.59	0.039	<0.05
Barraeau et al. [18]	5115	France	Cefuroxime	1.24	0.44	<0.0001
Tan et al. [19]	50,177	Singapore	Cefazolin	0.064	0.01	<0.001
Shorstein et al. [20]	16,264	USA	Multiple	0.31	0.014–0.14	Not reported
Friling et al. [22]	464,996	Sweden	Cefuroxime	0.39	0.027	<0.0001
Matsuura et al. [23]	34,752	Japan	Moxifloxacin	0.051	0.015	0.037
Beselga et al. [24]	15,689	Portugal	Cefuroxime	0.026	0	<0.05
Rahman et al. [25]	16,975	Ireland	Cefuroxime	0.26	0	<0.05
Katz et al. [26]	56,094	Israel	Cefuroxime	0.083	0.034	0.03
Jabbarvand et al. [27]	480,104	Iran	Cefuroxime	0.03	0	Not reported
Herrinton et al. [21]	315,246	USA	Multiple	0.07–0.14	0.044	Not reported
Haripriya et al. [28]	116,714	India	Moxifloxacin	0.07–0.08	0.02	<0.001
Creuzot-Garcher et al. [29]	6,371,242	France	Multiple	0.015	0.05	<0.001
Rudinisky et al. [31]	75,318	Canada	Multiple	0.03	0.03	0.90
Sharma et al. [32]	15,122	India	Cefuroxime	0.16	0.11	0.38

including the USA, and its use is variable even in nations where it is available. For example, intracameral antibiotics are used almost universally in Sweden, very commonly in France, but much less commonly in the UK, Spain, Germany, Belgium, Italy, the Netherlands, Poland, and Japan [39, 40]. A survey performed in Europe reported that 26% of surgeons were not using intracameral antibiotics routinely, and the main reason reported was the belief that intracameral antibiotics were unnecessary [41].

The American Society of Cataract and Refractive Surgery (ASCRS) reported a poll in which 1147 members participated [42]. Intracameral antibiotics were injected at the conclusion of surgery by 36% of all respondents. Further:

- The most common reported antibiotics directly injected were moxifloxacin (29% of all respondents) and vancomycin (22% of all respondents).
- The most common reported antibiotic mixed into the irrigating solution was vancomycin (15% of all respondents).

Intravitreal Injections

The incidence of endophthalmitis after intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents may differ depending on various factors. Large series have reported rates ranging from 0.02 to 0.3% per injection [43]. A 2016 series of 503,890 injections reported an overall rate of 0.036%, with no significant differences reported between aflibercept, bevacizumab, and ranibizumab [44]. However, the cumulative risk to each individual patient developing endophthalmitis is typically much higher because most patients may receive a series of injections. The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) reported a cumulative rate of 0.9% at 2 years [45].

Currently, no RCTs have evaluated alternative approaches for intravitreal injections. Therefore, only "guidelines" based on expert committees have been published [46, 47]. Current guidelines recommend the routine use of povidone-iodine on the ocular surface, reducing aerosolized droplets containing oral isolates and deferring treatment when active external ocular infections are present (Fig. 29.2). However,

Fig. 29.2 Photograph demonstrating an intravitreal injection. Note the eyelid speculum, the marking over the designated eye, and the evidence of povidone-iodine

Table 29.3 Selected reports of incidence of endophthalmitis with intravitreal injections (Adapted from Schwartz et al. [30])

Series	*n*	Nation	Rate without topical antibiotics (%)	Rate with topical antibiotics (%)	*p*-value
Bhatt et al. [50]	4767	USA	0.2	0.22	0.75
Bhavsar et al. [51]	8027	USA	0.03	0.13	0.25
Storey et al. [52]	117,171	USA	0.032	0.049	Not reported
Meredith et al. [53]	18,509	USA	0.015	0.04–0.08	0.2
Gregori et al. [54]	121,285	USA	0.02	0.013	0.38
Cheung et al. [55]	15,895	Canada	0.038	0.061–0.084	Not reported
Falavarjani et al. [56]	8037	Iran	0	0.01	0.3
Falavarjani et al. [57]	5091	Iran	0	0.1	0.18
Park et al. [58]	17,332	Korea	0.035	0	0.81
Li et al. [59]	90,339	USA	0.035	0.021	0.26
Ramel et al. [61][a]	11.450	France	0.2	0.03	0.024

[a]Significant changes in endophthalmitis rate

there is no consensus regarding the routine use of face masks, surgical drapes, eyelid speculums, conjunctival displacement, and the location of injection.

The ideal setting in which intravitreal treatments are performed remains unresolved. In the USA, most intravitreal injections are performed in the outpatient clinic. However, in some European nations, intravitreal injections are performed in an operating room or under similar aseptic conditions. A retrospective series, which directly compared patients injected in a clinic versus a different group of patients injected in an operating room, reported no significant differences in endophthalmitis rates [48].

The use of pre- or postinjection topical antibiotics varies widely [49]. Many retrospective series have reported no statistically significant difference in the rates of endophthalmitis with or without the use of topical antibiotics around the time of intravitreal injection (Table 29.3) [50–59, 61].

Of note, a series of 316,576 injections from France reported an overall rate of 0.021% and that prophylaxis with a topical antibiotic before and/or after injection was associated with a significantly higher rate [60]. Alternatively, a retrospective postinjection series from France reported a statistically significant reduction in endophthalmitis rates associated with topical antibiotics (0.03% vs. 0.23%; $p = 0.024$) [61].

In some series, the rates of endophthalmitis in patients treated with topical antibiotics are higher than in those treated without topical antibiotics. This may appear

counterintuitive but may be related to changes over time in conjunctival flora associated with topical antibiotic use [62, 63].

Surveys performed by the American Society of Retina Specialists (ASRS) have reported that members from outside the USA are more likely to use a face mask and use periprocedural topical antibiotics compared to US members [64–66]. The use of face masks is logical because of the high rate of oral flora isolated from cases of endophthalmitis. However, there have been no published trials comparing the use of face masks versus no face masks, and their use should be considered optional at this time.

Conclusion

The use of prophylactic antibiotics is controversial in many areas of ophthalmology and in many other areas of medicine. Some studies suggest that the prophylactic use of antibiotics may be associated with the development of resistance and subsequent colonization by more virulent isolates [67–69]. Antibiotic resistance rates may also be changing over time [70–73].

Preoperative preferred practice patterns for prophylaxis include povidone-iodine antisepsis, use of topical antibiotics, surgical draping, and properly sized and constructed incisions. Povidone-iodine is the only technique to achieve category II evidence in reducing the incidence of postoperative endophthalmitis [2]. Preoperative topical antibiotics reduce the conjunctival flora, but it is unclear if this actually affects endophthalmitis rates [62, 74].

Intraoperative sterile techniques to minimize endophthalmitis risk include correct and proper mixing of solutions and reduced posterior capsule rupture rates. Intracameral antibiotics remain the topic of debate because of the number needed to treat, cost-benefit analysis, and risk of increased bacterial antibiotic resistance.

At the present time, ophthalmologists in the USA appear less likely to use intracameral antibiotics for cataract surgery and less likely to use topical antibiotics with intravitreal injections. It is uncertain if there will be future convergence between the USA and other nations regarding these practices. The ASRS survey reports that many US ophthalmologists would use Aprokam or a similar approved intracameral antibiotic if it were available and reasonably priced [7].

It is estimated that about half of all antibiotics used are unnecessary or inappropriate, and antibiotic stewardship programs seek to correct this problem [75]. For example, the US Centers for Disease Control and Prevention have discouraged the routine use of vancomycin in surgical prophylaxis in view of emerging drug resistance [76]. New “antibiotic-resistant” bacteria are emerging and could emerge in ophthalmology.

There is only one RCT addressing intracameral antibiotics for cataract surgery, and there are no RCTs addressing antibiotic prophylaxis of intravitreal injections. There are conflicting results from observational studies and an unclear risk-benefit ratio. In general, antisepsis rather than antibiotics is preferred to reduce rates of endophthalmitis associated with both cataract surgery and intravitreal injections [77].

Postoperative topical antibiotic use also has failed to demonstrate any beneficial effect in prevention of postoperative endophthalmitis [78]. Similarly, the use of prophylactic oral antibiotics is controversial in this setting [79].

The use of preoperative povidone-iodine along with topical perioperative antibiotics has been a common standard practice, which reduces the ocular surface bacteria and may reduce the rates of endophthalmitis. Meticulous intraoperative sterile techniques and septic postsurgical management may also reduce endophthalmitis rates.

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Chapter 30
Guidelines for Safe Surgery

Taraprasad Das, Savitri Sharma, and Mudit Tyagi

Eye care-associated infections following intraocular surgery are not uncommon, but fortunately rare. There are three elements in any postoperative infection—the health personnel element, the surgical supply element, and the patient element. Though postoperative endophthalmitis are less common, there are several instances of cluster endophthalmitis. Unfortunately they are not very often reported, it is more difficult to confirm the source of such infection. These incidents prolong hospital stay, induce long-term disabilities, and add high costs to patients and their family. In addition to financial burden, it could often result in tragic loss of the eye. These misfortunes could be avoided by adopting safe practices both by the health-care personnel in one end and good manufacturing practices by the industry on the other end.

With a goal of "first do no harm," the World Health Assembly (WHA) in 2002 adopted a resolution, WHA55-18, urging all member states to strengthen the safety of health-care and monitoring systems. An international alliance was created in 2004 to recommend patient safety policies and practices. The "hand hygiene" was the first chosen challenge, and the WHO published the recommendations—"Clean Care is Safer Care, the WHO guidelines on Hand Hygiene in Health Care" [1]. The "safety of surgical care" was the second chosen challenge in years 2007–2008, and the WHO published the "Safe Surgery Saves Lives, the WHO guidelines for Safe Surgery" [2]. The basic belief is that most infections that occur after an intraocular surgery are preventable. This chapter will elaborate on the WHO published guidelines on the safety of patient care.

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Hand Hygiene

Hand hygiene is the primary measure to reduce infections. Transmission of pathogens occurs through physical contact or infected droplets dispersed in air. The primary process could be directly related to inadequate handwashing after getting in contact of the patients' contaminated skin or the immediate surrounding [3].

Nearly 10^6 skin squamous containing viable microorganisms are shed daily from normal skin. Hence it is natural that patient gowns, bed linen, bedside furniture, and other objects in the immediate environment of the patient become contaminated with patient flora [4, 5]. Following the contact with patients and/or a contaminated environment, microorganisms could survive on hands for 2–60 min. In the absence of hand hygiene, the degree of contamination is proportionate to the duration of care. Microbial transmission is likely to occur when the health-care workers fail to clean their hands effectively during one patient or between multiple patients care.

Handwashing Indications

The WHO handwashing ranking system and indications for handwashing are shown in Table 30.1 [1]. This is based on the recommendation of the Healthcare Infection Control Practices Advisory Committee (HICPAC) of the Center for Disease Control and Prevention (CDC), Atlanta, Georgia, USA. Typically there are two agents for hand hygiene—(1) alcohol-based hand rub and (2) soap and water.

Hand Hygiene

The WHO recommendations for the hand hygiene technique are as follows:

Alcohol-based hand rub—apply a palmful of required solution and cover all surfaces of the hands. Rub hands until dry.

Soap and water—wet hands with water and apply soap necessary to cover all surfaces. Rinse hands with water and dry thoroughly with a single-use towel. Use clean, running water whenever possible and avoid using hot water, as repeated exposure to hot water may increase the risk of dermatitis.

Surgical Hand Preparation

The WHO recommendations for surgical hand preparation technique are as follows:

1. Remove rings, wristwatch, and bracelets before beginning surgical hand preparation. Artificial nails are prohibited.

Table 30.1 The WHO ranking system and indications in hand hygiene [1]

Category	Criteria	Indication
IA	Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiological studies	Alcohol hand rub—routine hand antisepsis in all clinical situations if hands are not visibly soiled Soap and water—after contact with body fluids or excretions, mucous membranes, non-intact skin, or wound dressing
IB	Strongly recommended for implementation and supported by some experimental, clinical, or epidemiological studies and a strong theoretical rationale	Soap and water—when visibly dirty or soiled with blood or other body fluids Alcohol hand rub/soap and water—if exposure to potential spore-forming pathogens is strongly suspected or proven, including outbreaks of *C. difficile* Alcohol hand rub—before and after touching patient Alcohol hand rub/soap and water—before handling an invasive device for patient care, regardless of whether or not gloves are used Alcohol hand rub/soap and water—if moving from a contaminated body site to another body site during care of the same patient Alcohol hand rub—after contact with inanimate surfaces and objects (including medical equipment) in the immediate vicinity of the patient Alcohol hand rub—after removing sterile or nonsterile gloves Alcohol hand rub/soap and water—before handling medication or preparing food
IC	Required for implementation as mandated by federal and/or state regulation or standard	
II	Suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale or the consensus of a panel of experts	Soap and water—after using the toilet

2. Sinks should be designed to reduce the risk of splashes.
3. If visibly soiled, wash hands with plain soap before surgical hand preparation. Remove debris from underneath fingernails using a nail cleaner, preferably under running water.
4. Brushes are not recommended for surgical hand preparation.
5. If quality of water is not assured in the operating room, surgical hand antisepsis using an alcohol-based hand rub is recommended before donning sterile gloves when performing surgical procedures.
6. When using an antimicrobial soap, scrub hands and forearms for the length of time recommended by the manufacturer, typically 2–5 min. Long scrub times (e.g., 10 min) are not necessary.
7. When using an alcohol-based surgical hand rub with sustained activity, follow the manufacturer's instructions for application times. Apply the product to dry hands only. Do not combine surgical hand scrub and surgical hand rub with alcohol-based products sequentially.
8. When using an alcohol-based hand rub, use sufficient quantity to keep hands and forearms wet with the hand rub throughout the surgical hand preparation procedure.
9. After application of the alcohol-based hand rub as recommended, allow hands and forearms to dry thoroughly before donning sterile gloves.

The Use of Gloves

The WHO has laid down various procedures for the use of gloves in order to prevent infection. Two main reasons of wearing medical gloves are (1) to protect hands of health-care workers with blood and other body fluids and (2) to reduce transmission of infection either from patient to patient or through the health-care workers. The following points must be remembered in connection with the use of gloves.

(a) The use of gloves does not replace the need for hand hygiene by either hand rubbing or handwashing.
(b) Wear gloves when it can be reasonably anticipated that contact with blood or other potentially infectious materials, mucous membranes, or non-intact skin will occur.
(c) Remove gloves after caring for a patient. Do not wear the same pair of gloves for the care of more than one patient.
(d) When wearing gloves, change or remove gloves during patient care if moving from a contaminated body site to either another body site (including non-intact skin, mucous membrane, or medical device) within the same patient or the environment.

(e) The reuse of gloves is not recommended. In the case of glove reuse, implement the safest reprocessing method.

Along with the development of the guidelines, the WHO also suggested five implementation strategies. These included (1) a system change that ensures that the necessary infrastructure is in place such as access to safe water, continuous water supply, and availability of soap and towels, (2) training and education reinforcing the value and technique of hand cleaning (my five moments of hand hygiene), (3) periodic evaluation and feedback, (4) placing reminders in the workplaces, and (5) creating a right institutional environment of both awareness and priority.

The five moments of hand hygiene include encouraging the health-care workers to clean their hands (1) before touching a patient, (2) before clean/aseptic procedures, (3) after body fluid exposure/risk, (4) after touching a patient, and (5) after touching patient surroundings (Fig. 30.1).

Knowledge of the properties and activities of the antimicrobial agents is necessary for an intelligent choice (Table 30.2).

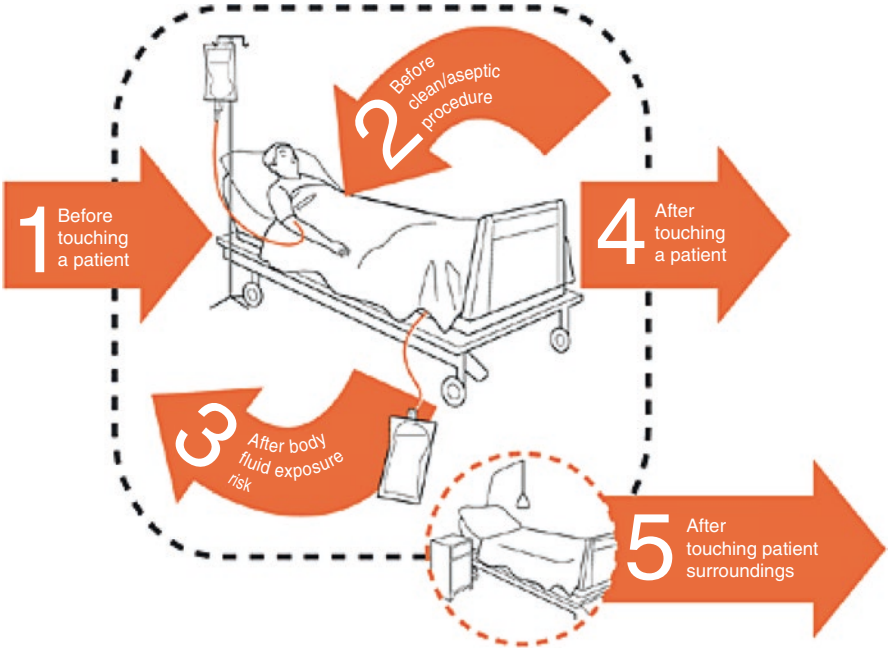


Fig. 30.1 My five moments of hand hygiene (with permission from WHO Guidelines on Health Hygiene in Health Care 2009; http://www.who.int/qpsc)

Table 30.2 The antimicrobial activity and summary of properties of antiseptics used in hand hygiene [1] (with permission from WHO Guidelines on Health Hygiene in Health Care 2009; http://www.who.int/qpsc)

Antiseptics	Gram-positive bacteria	Gram-negative bacteria	Viruses enveloped	Viruses non-enveloped	Mycobacteria	Fungi	Spores
Alcohols	+++	+++	+++	++	+++	+++	–
Chloroxylenol	+++	+	+	±	+	+	–
Chlorhexidine	+++	++	++	+	+	+	–
Hexachlorophene[a]	+++	+	?	?	+	+	–
Iodophors	+++	+++	++	++	++	++	±
Triclosan[a]	+++	++	?	?	±	±	–
Quaternary ammonium compounds	++	+	+	?	±	±	–

Antiseptics	Concentration	Speed of action	Residual activity	Use
Alcohols	60–80%	Fast	No	Hand rubbing
Chloroxylenol	0.5–4.0%	Slow	Contradictory	Handwashing
Chlorhexidine	0.5–4.0%	Intermediate	Yes	Hand rubbing and handwashing
Hexachlorophene[a]	3%	Slow	Yes	Handwashing, usually not recommended
Iodophors	0.5–10.0%	Intermediate	Contradictory	Handwashing
Triclosan[a]	0.1–2%	Intermediate	Yes	Handwashing, seldom used
Quaternary ammonium com		Slow	No	Hand rubbing and handwashing, seldom used

[a]Bacteriostatic; +++, good; ++, moderate; +, poor; ±, variable; –, none

Surgical Pause

The WHO guidelines for safe surgery strongly recommend "time out" or "surgical pause" [6]. This is a brief, 1-min or so pause, in the operating room activity immediately before the start of the surgery, at which time all members of the operating team verbally confirm the identity of the patient, the operation site, and the procedures to be performed. This is essentially to avoid "wrong-site" and "wrong-patient" errors. In general a signage of NISE is recommended in eye operating room. NISE is acronym for the following:

Table 30.3 Essential objectives in safe surgery [2]

1. The team will operate on the correct patient at the correct site
2. The team will use methods known to prevent harm from administration of anesthetics, while protecting the patients from pain
3. The team will recognize and effectively prepare for life-threatening loss of airway or respiratory function
4. The team will recognize and effectively prepare for risk of high blood loss
5. The team will avoid inducing an allergic or adverse drug
6. The team will consistently use methods known to minimize the risk for surgical site infection
7. The team will prevent inadvertent retention of instruments and sponges in surgical wounds
8. The team will secure and adequately identify all surgical specimens
9. The team will effectively communicate and exchange critical information for safe conduct of the operation
10. Hospital and public health systems will establish routine surveillance of surgical capacity, volume, and results

- *N*—name. This is confirmed by his/her name.
- *I*—identity. The address and other details of the patient are confirmed. Remember that there could be two people with the same name.
- *S*—surgery. The name of surgery is read out and confirmed with the patient.
- *E*—eye. The laterality of the eye is confirmed.

Objectives of Safe Surgery

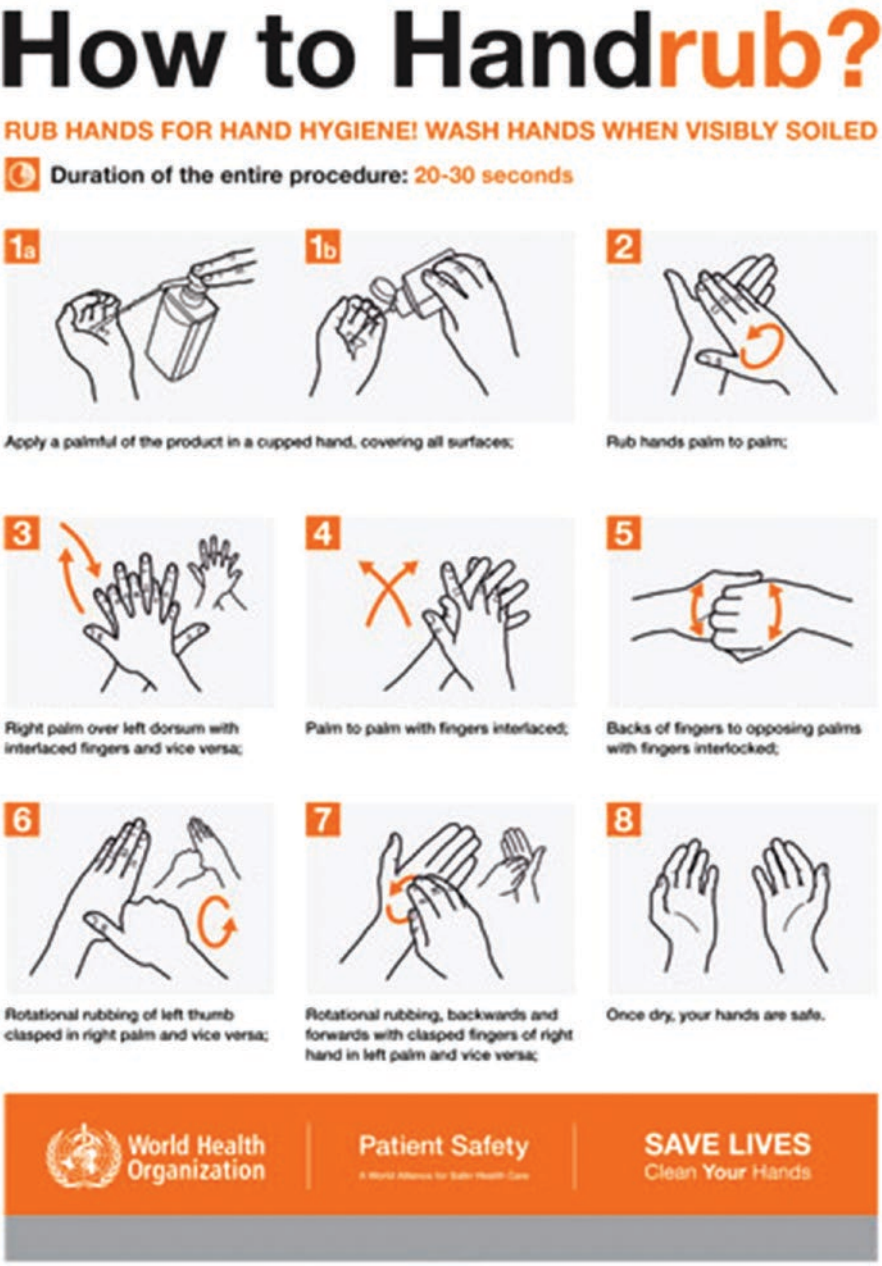
A safe intraoperative care involves a routine sequence of events—prevention of surgical site infection, safe anesthesia, and safe surgical team (Table 30.3) [2].

All abovementioned factors may not be applicable to eye surgery under local anesthesia though the basic tenants of "safe surgery" and "do no harm" do not change. "Time out" and "surgical checklist" are important measures to ensure safe surgery.

Appendix

With permission from WHO Guidelines on Health Hygiene in Health Care 2009; http://www.who.int/qpsc

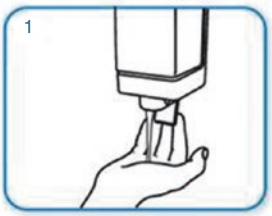
Appendix 1



Hand rub

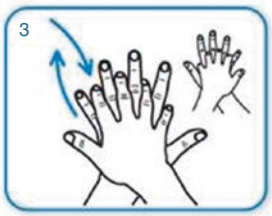
Appendix 2

Wet hands with water



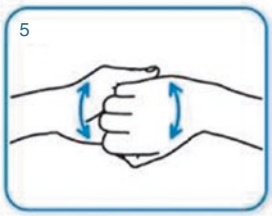
apply enough soap to cover all hand surfaces.

Rub hands palm to palm



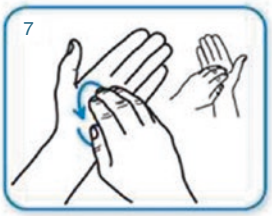
right palm over left dorsum with interlaced fingers and vice versa

palm to palm with fingers interlaced



backs of fingers to opposing palms with fingers interlocked

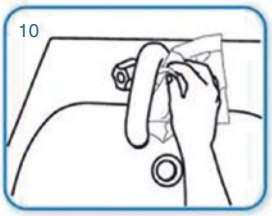
rotational rubbing of left thumb clasped in right palm and vice versa



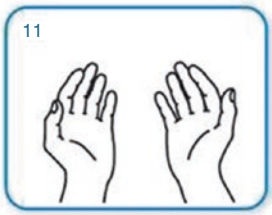
rotational rubbing, backwardds and forwards with clasped fingers of right hand in left palm and vice versa.

Rinse hands with water

dry thoroughly with a single use towel



use towel to turn off faucet



...and your hands are safe.

Handwash

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Part VII
Clinical Trials in Endophthalmitis

Chapter 31
Clinical Trials in Endophthalmitis

Taraprasad Das

Clinical trials evaluate how well a new medical approach works in people. Each trial answers scientific questions and tries to find better ways to prevent, screen for, diagnose, or treat a disease. Clinical trials may also compare a new treatment to a treatment that is already available. Every clinical trial has a protocol for conducting the trial. The randomized clinical trial (RCT) is the most powerful trial to decide the benefit of one treatment over the other. It is often considered the gold standard. The great value of RCT lies in the act of randomizing patients to receive or not receive the intervention when all other possible causes are equal between the two groups so that any significant differences between the groups in the outcome event could be attributed to the intervention and not to some other unidentified factor. Many randomized controlled trials involve large sample size because many treatments have relatively small effects. Obtaining statistically significant differences between two samples is easy if large differences are expected. The randomization procedure gives the randomized controlled trial its strength. Random allocation means that all participants have the same chance of being assigned to each of the study groups.

Despite the facts that the RCTs are best to resolve some of the treatment and prevention issues in endophthalmitis management, there are not many studies in the management of endophthalmitis. One of the reasons is its less often occurrence after an intraocular surgery. Too many factors are involved in post-trauma infection that an RCT of post-traumatic endophthalmitis is not possible. The most accepted treatment of infective endophthalmitis is the intravitreal antibiotic [1]. Other ancillary treatments are vitrectomy in established cases and preoperative/intraoperative antibiotics to prevent infection.

According to Jadad, randomized controlled trials can be classified as per the intervention that investigators want to explore, the way the participants are exposed to the intervention, the number of participants included in the study, whether the investigators and participants know which intervention is being assessed, and

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whether the preference of nonrandomized individuals and participants has been taken into account in the design of the study. Basically there are two broad kinds of trials—explanatory and pragmatic [2] (Table 31.1).

In practice, most randomized controlled trials combine elements of both—explanatory and pragmatic trials.

The various descriptions of trials are related to the expected outcomes, participant's exposure, and masking. They are shown in Table 31.2.

There are not many randomized trials in endophthalmitis. It is mostly because of the paucity of disease. In this section we have elaborated four randomized studies in post-cataract surgery endophthalmitis management, two large multicenter studies, and two single-center studies that we think have influenced the current management of endophthalmitis and, at least, the post-cataract surgery endophthalmitis. Two of them are in areas of treatment—the Endophthalmitis Vitrectomy Study (multicenter)

Table 31.1 Trial designs

Design	Purpose
Explanatory	Designed to answer a simple question: does the intervention work? If yes, how does it work?
Pragmatic	Designed to determine if the intervention works and also describes all the consequences of the intervention and its use under circumstances corresponding to daily practice

Table 31.2 Phases and designs of clinical trials

Phase		When	What
Phase	1	Safety study in human volunteers	After the animal safety is proven, phase 1 is performed in healthy volunteers; this phase of clinical trial documents the safety of the intervention in humans
	2	Efficacy and safety in human subjects	Evaluates the efficacy of the intervention while still providing information on safety
	3	Effectiveness study	Randomized trials to assess the effectiveness of the intervention
	4	Post-marketing study	Identifies and monitors possible adverse events not yet documented
Design	Parallel	Each group of participants is exposed to only one of the study interventions	
	Crossover	Each of the participants, randomly assigned order, is given all of the study interventions in successive periods	
	Factorial	Two or more experimental interventions are evaluated separately and also in combination and against a control	
Masking	Open	Everybody involved in the trial knows which intervention is given to each participant	
	Single masked	A group of individuals involved in the trial (usually patients) does not know which intervention is given to each participant	
	Double masked	Two groups of individuals involved in the trial (usually patients and treating physicians) do not know which intervention is given to each participant	

and dexamethasone in bacterial endophthalmitis study (single center)—and two of them are in areas of prevention, the European Society of Cataract and Refractive Surgeons' prevention of endophthalmitis study (multicenter) and povidone-iodine prophylaxis study (single center). Some other studies such as the Complete and Early Vitrectomy in Endophthalmitis (CEVE) and Collaborative Bleb-Related Infection study are mentioned in relevant places (Table 31.3).

Table 31.3 Summary of clinical trials in endophthalmitis

Area	Study question	Study	Study type	Answer
Prevention	Does povidone reduce the incidence of postoperative intraocular surgery endophthalmitis?	Povidone-iodine prophylaxis study	Single-center open-level nonrandomized study	Preoperative application of povidone-iodine to ocular surface reduces the incidence of post intraocular surgery endophthalmitis [3]
	Does intraoperative intracameral cefuroxime reduce the incidence of post-cataract surgery endophthalmitis?	ESCRS prevention of endophthalmitis after cataract surgery	Multicenter randomized controlled study	Intracameral cefuroxime reduces the incidence of culture-positive endophthalmitis following cataract surgery [4]
Treatment	Does preoperative intravenous antibiotic reduce endophthalmitis risk after cataract surgery?	Endophthalmitis Vitrectomy Study (EVS)	Multicenter randomized controlled study	Preoperative systemic antibiotics do not influence the endophthalmitis outcome [1]
	Do all eyes with endophthalmitis need immediate vitrectomy?			Patients with vision of hand motions (measured at 1 m from the patient) could have equal benefit from vitreous biopsy and intravitreal antibiotics and do not necessarily need an immediate vitrectomy [1]
	Is addition of intravitreal dexamethasone beneficial in postoperative endophthalmitis?	Dexamethasone in endophthalmitis study	Single-center randomized study	Additions of intravitreal dexamethasone to intravitreal antibiotics help reduce inflammation without affecting the visual outcome [5]

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Chapter 32
Endophthalmitis Vitrectomy Study

Taraprasad Das

The Endophthalmitis Vitrectomy Study (EVS) was a randomized, multicenter, clinical trial designed to determine the role of immediate pars plana vitrectomy and the role of systemic antibiotics in the management of acute endophthalmitis following cataract surgery or secondary intra ocular lens (IOL) implantation surgery [1]. The inclusion and exclusion criteria are shown in Table 32.1.

Treatment Assignment

The eligible patients were assigned at random to a 2 × 2 factorial design to one of the four treatment groups (Table 32.2).

Treatment Strategy

Treatment was initiated within 6 h of initial examination. In all four groups, undiluted vitreous specimen was collected before performing the assigned procedure, usually with a vitreous cutter in the VIT group and using a needle in the TAP group. Patients assigned to VIT received a three-port pars plana vitrectomy, and no additional attempt was done to separate the posterior vitreous, if not separated already. A vitreous volume of 0.1–0.3 ml was collected in patients assigned to TAP. Two intravitreal antibiotics were injected in all four groups, vancomycin 1.0 mg in 0.1 ml and amikacin 0.4 mg in 0.1 ml. Patients assigned to intravenous (IV) antibiotics received ceftazidime and amikacin.

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Table 32.1 Inclusion and exclusion criteria in the EVS

Inclusion criteria	Exclusion criteria
Visual acuity—light perception (LP) or better and worse than 36 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) acuity chart placed at 4 m (equivalent to approximately 20/50 or worse)	Known eye disease limiting visual acuity to 20/100 before development of cataract
Sufficient clarity of the cornea and anterior chamber of the involved eye to allow visualization of at least some part of the iris	Prior intraocular surgery other than cataract or IOL surgery
Sufficient clarity of the cornea to perform pars plana vitrectomy	Prior penetrating ocular trauma
A hypopyon or sufficient clouding of the anterior chamber or vitreous to obscure a view of second-order retinal arterioles	Previous injection of intravitreal antibiotics
	Prior pars plana vitrectomy, retinal detachment, or moderately high choroidal detachment, as judged by indirect ophthalmoscopy or ultrasound
	Probable intolerance to any study drugs (with exception of penicillin allergy, in which case alternatives to beta-lactam drugs were used)
	Strong suspicion of fungal endophthalmitis

Table 32.2 Two-by-two factorial design in the EVS

Group VIT-IV	*Group VIT-NOIV*
Initial vitrectomy (VIT) Intravenous antibiotics (IV)	Initial vitrectomy (VIT) No intravenous antibiotic (NO IV)
Group TAP-IV Initial tap or biopsy (TAP) Intravenous antibiotics (IV)	*Group TAP-NOIV* Initial tap or biopsy (TAP) No intravenous antibiotics (NO IV)

Culture

Undiluted vitreous and vitrectomy effluent, when vitrectomy was done, were cultured. Three media were used—chocolate agar (37 °C in CO_2), thioglycolate broth, and Sabouraud dextrose agar. The vitrectomy effluent was filtered through a sterile 0.45 μm membrane filter; the filter was divided into three pieces under sterile conditions. The three pieces of filter papers were cultured in chocolate agar, in Sabouraud dextrose agar, and thioglycolate broth. Gram stain was used for microscopy. The microbiological results were categorized into "confirmed positive," "equivocal," and "negative." The microbiology and infection category is shown in Table 32.3 [2].

In the EVS there was 69.3% (n = 291) confirmed growth, 12.9% (n = 54) was equivocal growth, and 17.9% (n = 75) was no growth. Gram-positive cocci were more common (94.2%) than gram-negative bacilli (5.9%), and gram-positive coagulase-negative micrococci were the most common isolation (n = 226; 70%).

Table 32.3 Microbiology and infection category in EVS

	Confirmed positive	Equivocal	Negative
Microbiology category	At least semi-confluent (≥11 cfu growth on at least one solid medium) Growth in two or more media Growth in two media, one from the vitreous/AC fluid sample and the other from vitrectomy cassette	Any growth <11 cfu	No growth in any medium
Infection category	Confirmed positive culture Equivocal culture + positive Gram stain of corresponding tinctorial properties	Equivocal culture + gram stain equivocal or negative Gram stain positive, culture negative	No growth in any medium

Adapted from [2]
AC anterior chamber, *cfu* colony-forming unit

Table 32.4 Susceptibility of organisms to trial drug combinations in EVS

Drug combination		Possible routes in EVS	Total no. of isolates	No isolates susceptible to at least one drug
Vancomycin	Amikacin	Intravit/subconj	321	319 (99.4%)
Vancomycin	Ceftazidime	Subconj	321	319 (99.4%)
Amikacin	Ciprofloxacin	Systemic	320	287 (89.7%)
Amikacin	Ceftazidime	Systemic	318	281 (88.4%)

Intravit intravitreal, *Subconj* subconjunctival
Adapted from [2]

All gram-positive coagulase-negative micrococci were sensitive in descending order to vancomycin (100%), amikacin (86.1%), and ciprofloxacin (77.9%); gram-negative bacilli were sensitive in descending order to ciprofloxacin (94.7%) and both ceftazidime and amikacin (89.5% each). In nearly all instances, the study drug combination was sensitive to the isolates in the EVS (Table 32.4).

Study Medications

The EVS used medicines through all routes—topical, subconjunctival, intravitreal, and systemic (intravenous or oral). These consisted of antibiotics, vancomycin, ceftazidime, amikacin, and ciprofloxacin, and corticosteroids, dexamethasone and prednisolone. The details and route of delivery are shown in Table 32.5.

Summary of Major Results

In the EVS 420 patients were recruited in 24 study centers. The major results are tabulated in Table 32.6 [3].

Table 32.5 EVS medicines and routes of delivery

Drug	Route			
	Intravitreal	Subconj	Systemic	Topical
Vancomycin	1.0 mg/0.1 ml	25 mg/0.5 ml	x	50 mg/ml
Amikacin	0.4 mg/0.1 ml	25 mg/0.1 ml	7.5 mg/kg IV 1, then 6 mg/kg IV q 12 h for 5–10 days	20 mg/ml
Ceftazidime	x	x	2 g IV q8h for 5–10 days	x
Dexamethasone	x	6 mg/0.25 ml	x	x
Ciprofloxacin	x	x	750 mg PO twice daily (if allergic to penicillin) for 5–10 days	x
Prednisone	x	x	30 mg PO twice daily for 5–10 days	
Delivery schedule	During of VIT/TAP	At end of VIT/TAP	Post VIT/TAP	Post VIT/TAP

Table 32.6 EVS major results

Category	Results
Symptoms	Reduced vision. 26% had LP only; 12% had afferent pupillary defect; 5% had corneal ring ulcer Pain was absent in 25% patients
Signs	Hypopyon. 86% patients had hypopyon
Culture	Culture positivity rate: 69.3% (n = 291) 68% gram-positive coagulase-negative organisms 22% other gram-positive organisms 6% gram-negative organisms 4% poly-bacterial infection
Higher rate of confirmed growth gram-positive coagulase-negative micrococci	Diabetes mellitus was the only factor associated with significantly higher incidence of gram-positive coagulase-negative micrococci (58.6%)
Baseline features of higher confirmed growth	Five factors correlated with higher rates (84.5%) of gram negative and gram positive (other than coagulase-negative micrococci) include: • Corneal infiltrate • Cataract wound abnormalities • Afferent pupillary defect • Loss of red reflex • Light presentation vision at presentation • Symptoms onset with 2 days of cataract surgery

Table 32.6 (continued)

Category	Results		
Additional procedures	44 (10.5%) patients needed additional surgery within 7 days; 38 (9%) due to worsening intraocular inflammation/infection 31 (7.6%) needed reinjection of intravitreal antibiotics; all these patients were pooled from 44 patients (70.5%) Additional procedures were more often required in cases of gram-negative or gram-positive infection other than gram-positive coagulase-negative microorganism		
Media clarity and visual acuity outcome	Media cleared more quickly after vitrectomy than tap-biopsy		
	Final vision	% eyes	
	20/40 or better	53%	
	20/100 or better	74%	
	5/200 or better	11%	
	No LP	5%	
VIT vs. TAP visual acuity outcome	No statistical difference in the visual acuity outcome in VIT and TAP groups		
IV vs. NOIV visual acuity outcome	No statistical difference in the visual acuity outcome in IV and NOIV groups		
Visual acuity outcome by presenting vision	Presenting vision LP: greater chance of good vision with VIT compared to TAP		
	Final vision	VIT	TAP
	20/40	33%	11%
	20/100	56%	21%
	5/200	80%	53%
	Presenting vision HM: equal chance of good vision with both VIT and TAP		
	Final vision	VIT	TAP
	20/40	66%	62%
	20/100	86%	84%
	5/200	95%	97%
Visual acuity outcome by microbiology	Culture negative—better prognosis Gram positive coagulase negative—better prognosis Other gram positive—worse prognosis Gram negative—worse prognosis		

Visual Outcome Versus Microbiology

In general, patients with gram-positive coagulase-negative micrococci infection had better visual outcome compared to any other type of infection (Table 32.7). But the EVS concluded that the presenting vision was more powerful than the microbiologic factors in predicting the visual outcome [4].

Table 32.7 Visual outcome by microbiology results in the EVS

Visual outcome cumulative	Equivocal growth; $n = 123$		Gram-positive coagulase-negative micrococci; $n = 187$		Gram-positive others; $n = 56$		Gram negative; $n = 16$		Mixed; $n = 12$		p
	n	%	n	%	n	%	n	%	n	%	
≥20/40	68	55.3	115	61.5	16	28.6	7	43.8	3	25.0	<0.01
≥20/100	98	79.7	157	84.0	24	42.9	9	56.3	5	41.7	<0.01
>5/200	113	91.9	179	95.7	35	62.5	11	68.8	11	91.7	<0.01

Adapted from [4]

Table 32.8 Management recommendation based on the EVS data

Procedure	Presenting vision: ≤LP	Presenting vision: ≥HM
Vitreous culture	Yes	
VIT	Primary procedure	Secondary procedure
TAP	Secondary procedure	Primary procedure
Intravitreal antibiotics	Ceftazidime 2.25 mg in 0.1 ml Vancomycin 1 mg in 0.1 ml	
Systemic antibiotics	No	
Oral corticosteroid	Prednisone 30 mg/twice daily after intravitreal antibiotics for 5–10 days	

Cost Consideration

The EVS collected hospital charges from 30.7% ($n = 129$) patients and commented that both intravenous antibiotics and vitrectomy increased the hospital charges significantly. Vitrectomy without intravenous antibiotics was the most charge-effective treatment for patients presenting LP only presenting vision. Tap-biopsy was the most charge-effective treatment for patients presenting with HM or better presenting vision. Should the EVS recommendations are used for treatment of acute post-cataract/secondary IOL surgery, the estimated annual reduction in hospital charges in the USA would be between US$ 7.6 million (when incidence is 0.1%) and US$ 40 million (when incidence is 0.4%) [5].

Management Consideration

The EVS treatment recommendation was based on the presenting vision. It recommended vitrectomy for patients with presenting vision of LP or less and only vitreous biopsy + intravitreal antibiotics for patients presenting with hand motions (at 60 cm) or more. The study did not recommend the use of systemic antibiotics and did not test intravitreal corticosteroids. Based on the EVS data, one could consider vitrectomy irrespective of the presenting vision in patients with diabetes mellitus. Table 32.8 outlines the recommendations.

Frequently Asked Questions

1. *How was the vision measured in the EVS?*
   A: In the EVS visual acuity was tested at 4 m (ETDRS chart), at 1 m (count fingers), at 60 cm (for measurement of hand motions, HM), and at 0.9 meter (for measurement of light perception, LP). The recording of hand motions (HM) is important since this was the cutoff vision to decide between tap-biopsy and vitrectomy. To document HM the patient's opposite eye was occluded, and light source (such as a lamp used for near vision) was directed from behind the patient to the examiner's hand, either stationary or slowly moving vertically or horizontally, at a distance of 60 cm from the eye. The LP was documented by shining an indirect ophthalmoscope light set at maximum intensity at different directions placed at 0.9 m. Precise documentation of presenting vision could not be overemphasized since this alone determines the treatment strategy.

2. *Is it mandatory to inject two intravitreal antibiotics?*
   A: Two intravitreal antibiotics were injected in the EVS—one against gram-positive and the other against gram-negative infection. In the EVS gram cocci was the predominant infecting organism (94%), and gram-negative infection accounted for 6% cases only. Many studies outside the EVS have shown a higher rate of gram-negative infection [6, 7]. Hence it is considered wiser to inject two antibiotics, for gram-positive and gram-negative infection; only one culture sensitivity-adjusted antibiotic is injected in a repeat intervention.

3. *Why was ceftazidime chosen for intravitreal antibiotics when amikacin was the study drug?*
   A: Ceftazidime is a third-generation cephalosporin. It causes filamentation and eventually lysis of the cells due to its primary activity against PBP-3. Amikacin is an aminoglycoside antibiotic that works by binding to the bacterial 30S ribosome subunit, causing misreading of mRNA that leaves the bacterium incapable of synthesizing proteins vital for its growth. The susceptibility of ceftazidime and amikacin is almost similar; they both act against gram-negative infection. But aminoglycosides such as gentamicin and amikacin are reported to cause macular infarction [8, 9]. With increasing reports of ceftazidime resistance, a different intravitreal antibiotic, say imipenem, might replace ceftazidime as the first empiric treatment of endophthalmitis [10].

4. *Does EVS recommendations hold true for patients with diabetes mellitus?*
   A: In the EVS, 58 of 420 (13.8%) had diabetes mellitus. The microbiology spectrum and the visual outcome following treatment were different in the diabetic people compared to the nondiabetic people, so also the outcome [11] (Tables 32.9 and 32.10).

   Relative risk of poor visual acuity was 1.55 in diabetic patients in the EVS. The eyes in diabetic patients were more likely to have an additional procedure after initial intervention than the eyes of patients without diabetes (43.17% diabetics vs. 34% nondiabetics; $p = 0.18$). These findings suggest that

Table 32.9 Microbiology spectrum by diabetes status in EVS

Microbiology	Diabetics $n = 58$ (%)	Nondiabetics $n = 362$ (%)
Gram negative	2 (3.5)	17 (4.7)
Other gram positive	13 (22.4)	62 (17.1)
Gram positive, coagulase negative	34 (58.6)	163 (45.0)
No growth/equivocal growth	9 (15.5)	120 (33.2)

Table 32.10 Visual outcome by diabetic status in EVS

Visual acuity	Diabetics $n = 54$ (%)	Nondiabetics $n = 340$ (%)
<5/200	11 (20.4)	34 (10.0)
≥5/200	43 (79.6)	306 (90.0)
<20/100	24 (44.4)	77 (22.7)
≥20/100	30 (55.6)	263 (77.4)
<20/40	33 (61.1)	152 (4.7)
≥20/40	21 (38.9)	188 (55.3)

vitrectomy (with intravitreal antibiotics) could be the first choice of treatment of endophthalmitis in patients with diabetes mellitus. It is also necessary to closely observe these patients because the posttreatment course could be worse than the nondiabetic patients.

5. *What is the alternative to oral corticosteroid if it is contraindicated?*
A: Both infection and inflammation play a role in endophthalmitis. The microorganisms cause infection, and the exo-/endotoxins secreted by the microorganisms cause inflammation. As a general rule, gram-positive organisms secrete exotoxins, and the gram-negative organisms secrete endotoxins. These toxins invoke an acute inflammatory response. These pathologic processes ultimately culminate in fibrin membrane and possibly retinal necrosis. The treatment in a bacterial endophthalmitis must be designed to combat both infection and inflammation.

Corticosteroids have both anti-inflammatory and immunosuppressive effects. The anti-inflammatory effects are nonspecific and will inhibit the inflammatory reaction to nearly any type of stimulus. The use of corticosteroid therapy in managing endophthalmitis has been a controversial subject. In a prospective randomized trial, intravitreal dexamethasone was shown to reduce the degree of inflammation without affecting the final visual outcome [12]. Few retrospective studies have confirmed that intravitreal dexamethasone does not impact the final visual outcome [13, 14], and one study found it detrimental to good visual recovery [15].

Dexamethasone phosphate (400 μg) is the most commonly used intravitreal corticosteroid in most studies though one study has shown beneficial effect of intravitreal triamcinolone acetonide (4 mg) in the presence of appropriate antibiotics in culture-proven cases of *Pseudomonas* infection [16]. Experimental studies suggest intravitreal dexamethasone injection within 36 h of infection for the best effect [17].

6. *Could the EVS treatment recommendation be applied to other forms of postoperative and traumatic endophthalmitis?*
   A: The EVS recruited only acute bacterial and less severe endophthalmitis following cataract and secondary IOL surgery. Hence, it cannot be applied to any other forms of postoperative (such as chronic, fungal, and other post-intraocular surgery), trauma, and endogenous endophthalmitis. The Early and Complete Vitrectomy in Endophthalmitis (CEVE) study proposes that if the eye with good red reflex or with some retinal visibility does not benefit from intravitreal antibiotics and intravitreal corticosteroid in 24 h, it should receive a complete vitrectomy regardless of visual acuity. The rationale of early vitrectomy are it (1) allows immediate treatment of all treatable pathologies, (2) serves as a prophylactic measure preventing complications that would occur with a prolonged disease process, and (3) reduces the risk of surgery via improved visibility (as the disease progresses, the corneal transparency decreases due to increased corneal edema) and decreased tissue fragility (the less severe the existing pathology, the less likely the iatrogenic complications will occur). A complete vitrectomy includes separation of posterior hyaloid in the posterior pole, but staying short of the periphery, contrary to the recommendations of core vitrectomy in the EVS. The rationales of complete vitrectomy are that it reduces dramatically the inflammatory debris in the vitreous cavity and reduces the incidence and severity of macular complications. In a small series of 47 eyes, the CEVE study documented a 91% eyes regaining visual acuity of 20/40 or more compared to a 54% eyes that received vitrectomy in the EVS [18].

7. *Is the EVS recommendation valid two decades after it was published?*
   A: There is some disagreement to the presenting vision-based treatment protocol and the type of vitrectomy. Because the post-cataract surgery endophthalmitis is a dynamic process, it is appropriate to classify it as “early” and “advanced”; it could be prudent to consider intravitreal antibiotics only in early cases (and convert to vitrectomy if it does not respond in a day or two) and subject to vitrectomy in advanced cases.

   A lot of technical and technological advancement have occurred in vitrectomy in last two decades. The current safety features of vitrectomy are derived from smaller gauge vitrectomy probes, placement of the cutting port closer to the probe tip, variable cut rate, and better fluid dynamics. Coupled with better viewing system, one could go closer to the retina than before. It is argued that these technological advances should allow the surgeon a complete vitrectomy instead of a core vitrectomy (where 50% of vitreous is left behind) and, if required, also insert silicone oil at the conclusion of complete vitrectomy whenever a retinal detachment is suspected [19]. Endoscopic vitrectomy is also a new option in a very severe endophthalmitis [20].

   Additionally, superior drugs are now available that have a better intravitreal penetration after systemic therapy. These could be possibly be used in management of infectious endophthalmitis.

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Chapter 33
European Society of Cataract and Refractive Surgeons' Antibiotic Prophylaxis Study in Cataract Surgery

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The European Society of Cataract and Refractive Surgeons (ESCRS) antibiotic prophylaxis study in cataract surgery was a multicenter randomized clinical trial done in 24 ophthalmic facilities of 9 European countries—Austria, Belgium, Germany, Italy, Poland, Portugal, Spain, Turkey, and the United Kingdom. The ESCRS study evaluated the effect of intracameral injection of cefuroxime 1 mg in 0.1 ml at the conclusion of cataract surgery and compared post cataract surgery endophthalmitis rates with other study groups that included postoperative topical antibiotics and controls. It was planned that 35,000 patients receiving cataract surgery would be recruited and the patients would be randomized to one of four treatment groups (Table 33.1). The ESCRS study started in September 2003 and prematurely terminated in January 2006 when the Data Monitoring Committee was satisfied with the significant benefit from use of one of two antibiotics.

Table 33.1 Study design [1]

Inclusion criteria	Exclusion criteria
Phacoemulsification cataract surgery with IOL implantation as a single procedure without any additional surgery	Patients under 18 years of age Patients allergic to penicillin and cephalosporins Patients in long-term nursing homes Pregnant patients

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Group A Placebo vehicle drops x 5* No intracameral injection No perioperative antibiotics	Group B Placebo vehicle drops x 5* Intracameral cefuroxime injection
Group C Levofloxacin drops 0.5% x 5* No intracameral injection	Group D Levofloxacin drops 0.5% x 5* Intracameral cefuroxime injection

*One drop 60 minutes before surgery; 1 drop 30 minutes before surgery; 3 drops at 5-minute intervals commencing immediately after surgery.

Fig. 33.1 Treatment assignment in ESCRS antibiotic prophylaxis study in cataract surgery.

Treatment Assignment

The study was planned as 2 × 2 factorial design to test for the effects of two prophylactic antibiotics: (1) intracameral antibiotic injected at the conclusion of incident-free phacoemulsification cataract surgery and (2) topical levofloxacin in perioperative period (Fig. 33.1).

The study medications are listed in Table 33.2.

Case Definition

A diagnosis of presumed endophthalmitis was made for any patient presenting with pain or loss of vision thought to be due to infection. Samples of aqueous and vitreous were collected from these patients and investigated using three microbiology methods—microscopy (Gram stain), culture, and molecular method (Polymerase Chain Reaction (PCR) using nonspecific microbial primers). Infective endophthalmitis was labeled if one of the three methods was positive. Each unproven case was reviewed for evidence of toxic anterior segment syndrome (TASS).

Results [2]

A total of 16,603 patients were recruited to the study, and the intent to treat (ITT) was 16,211 patients. This consisted of the following (Table 33.3).

Twenty-nine patients in the ESCRS study developed clinical endophthalmitis; 20 (69%) were microbiology positive, and they grew 23 microorganisms including two

Table 33.2 Study medications

Medication	Preoperative	Intraoperative	Postoperative
Povidone iodine. Topical	Povidone iodine 5%. Onto conjunctival sac and onto cornea for 1 min, 3 min before surgery	×	×
Levofloxacin Topical	Levofloxacin 0.5% One drop at 60 min and 30 min before surgery	×	Levofloxacin 0.5% One drop at 5 min interval commencing immediately after surgery One drop every 6 h for 6 days starting a day after the surgery
Cefuroxime Intracameral	x	Cefuroxime intracameral 1 mg in normal saline	×

Table 33.3 ITT in the ESCRS study

Group	Treatment	*n*
Group A	Placebo topical + no intracameral antibiotic	4050
Group B	Placebo topical + yes Intracameral antibiotic	4056
Group C	Levofloxacin topical + no intracameral antibiotic	4049
Group D	Levofloxacin topical + yes intracameral antibiotic	4052

patients who developed polybacterial infection (Fig. 33.2). The highest incidence of endophthalmitis was seen in Group A (placebo topical; no intracameral antibiotic)—total endophthalmitis, 0.345% (95% CI, 0.119–0.579%), and proven endophthalmitis: 0.247% (95% CI, 0.118–0.453%). The lowest incidence of endophthalmitis was in group D (perioperative topical levofloxacin + intracameral cefuroxime)—total, 0.049% (95% CI, 0.006–0.181); proven: 0.025% (95% CI, 0.001–0.139).

In a multivariate regression analysis, the following factors were found to impact in occurrence of endophthalmitis (Table 33.4).

Study Recommendations

The ESCRS study recommended routine use of intracameral cefuroxime 1 mg in 0.1 ml at the conclusion of cataract surgery in addition to preoperative preparation with 5% povidone iodine and postoperative topical levofloxacin.

Group A **Placebo vehicle drops x 5*** **No intracameral injection** **No perioperative antibiotics** **No. endophthalmitis = 14** (Proven= 10; Unproven= 4) **Intent to treat** Number of patients: 4054 **Incidence rates (%)** Total: 0.345; Proven: 0.247 2 *Streptococcus pneumonia* 1 *Streptococcus salivaritus* 1 *Streptococcus suis* 1 *Streptococcus mitis, Staphyloccus epidermidis,* 1 *Staphylococcus aureus, Stphylococcus epidermidis, Propianobacterium acnes* 3 *Staphyloccus epidermidis* 1 *Propianobacterium acnes* 4 non-proven	**Group B** **Placebo vehicle drops x 5*** **Intracameral cefuroxime injection** **No. endophthalmitis = 3** (Proven 2; Unproven 1) **Intent to treat** Number of patients: 4056 **Incidence rates (%)** Total: 0.074; Proven: 0.049 2 *Stphylococcus epidermidis* 1 non-proven
Group C **Levofloxacin drops 0.5% x 5*** **No intracameral injection** **No. endophthalmitis = 10** (Proven = 7; Unproven = 3) **Intent to treat** Number of patients: 4049 **Incidence rates (%)** Total: 0.247; Proven:0.173 1 *Streptococcus salivaritus* 1 *Streptococcus sanguinis* 1 *Streptococcus oralis* 1 *Staphylococcus aureus* 2 *Staphylococcus epidermidis* 1 *Staphylococcus hominis* 3 Non-proven	**Group D** **Levofloxacin drops 0.5% x 5*** **Intracameral cefuroxime injection** **No. endophthalmitis = 2** **(**Proven = 1; Unproven = 1) **Intent to treat** Number of patients: 4052 **Incidence rates (%)** Total: 0.049; Proven: 0.025 **1** *Staphylococcus warneri* 1 Non-proven

Fig. 33.2 ESCRS study. Endophthalmitis and microbiology results

Table 33.4 Factors influencing endophthalmitis in ESCRS Study

Factors	Odds to developing endophthalmitis
Clear corneal incision	5.88 times for patients receiving a clear corneal procedure
Surgical complications	4.95 times for patients with intraoperative surgical complications
Intracameral cefuroxime	4.92 times for patients not receiving intracameral cefuroxime at conclusion of cataract surgery
IOL optic material	3.13 times for patients receiving a silicone optic material

Frequently Asked Questions

1. *Is intracameral antibiotic mandatory in all cases of cataract surgery?*
   A: In an experimental study, we had shown that vancomycin helps reduce *Staphylococcus epidermidis* adherence to polymethyl methacrylate (PMMA) intraocular lens (IOL) irrespective of the vancomycin treatment time of the IOL, before or after dipping in solution of the microorganism [3]. Despite the ESCRS publication [2], currently the use of intracameral antibiotic is not universal. The reasons are (a) fear of dilution errors, (b) toxic anterior segment syndrome (TASS), (c) emergence of resistant organisms, (d) associated retinal vascular toxicity (with aminoglycosides), and hemorrhagic occlusive retinal vasculitis (with vancomycin).

   In a 2012 Singapore nationwide survey, close to 70% of cataract surgeons who responded admitted to not using any intracameral antibiotic. In addition to the fear of toxicity, the effort of antibiotic preparation, and additional cost, many did not agree with the benefit of this procedure [4]. At the same time, 54% stated to consider to using intracameral antibiotic routinely should such a ready-to-use preparation were available. In 2012 specific commercial cefuroxime sodium at the necessary concentration (0.1 mg/ml) for intracameral use, called Aprokam® (Laboratoires Théa, Clermont-Ferrand, France), received approval by the European Medicines Agency (EMA) and was introduced to European market. By now it is officially approved for intracameral antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery in 24 European countries (includes eight countries where the study patients were recruited, except Turkey). A survey performed in Europe, at least a year after the commercial availability of intracameral cefuroxime, reported that 26% of surgeons were not using intracameral antibiotics routinely, and the main reason reported was the belief that intracameral antibiotics were unnecessary [5]. In 2014, 7 years after the publication of the ESCRS recommendations, the American Society of Cataract and Refractive Surgery (ASCRS) reported a poll in which 1147 members participated [6]. Intracameral antibiotics were injected at the conclusion of surgery by only 36% of all respondents.

   Cefuroxime is not unique in intracameral use. Similar beneficial effect has been observed with use of intracameral moxifloxacin in one Indian prospective study [7], and another Indian prospective study using intracameral cefuroxime did not report statistically significant benefit [8]. Currently there is some controversy on routine use of intracameral antibiotic in every cataract surgery [9, 10].

2. *What are the other intracameral antibiotics?*

   A: Many other antibiotics have been used in the anterior chamber after cataract surgery. They include cefazolin and vancomycin in addition to cefuroxime and moxifloxacin.

   In one study, intracameral cefazolin, 2.5 mg in 0.1 ml, reduced endophthalmitis from 0.422% to 0.047% and culture-proven endophthalmitis from 0.388% to 0.032%; there was 8.89-fold of risk reduction of endophthalmitis with use of intracameral cefazolin [11]. In another study, intracameral vancomycin, 1 mg in 0.1 ml, reduced endophthalmitis from 0.3% to 0.008%; there was 38-fold relative risk reduction of endophthalmitis with use of intracameral vancomycin [12]. But there are reports of hemorrhagic occlusive vasculitis presumably caused by intravitreal vancomycin [13].

3. *Are there any specific indications for intracameral antibiotic use?*

   A: In view of the fear for emergence of resistant organism with use of intracameral antibiotic, one could consider use in high-risk individuals receiving cataract surgery instead of a routine use. In absence of any specific guidelines, we use intracameral antibiotic in high-risk situations. Some of the high-risks indications include posterior capsule break during cataract surgery, those patients where anterior vitrectomy was part of the surgery, in prolonged (>40 min) and difficult surgery (such as excessive iris manipulation), corneal surface disorders, and very elderly (≥80 years) individuals.

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Chapter 34
Povidone-Iodine Prophylaxis in Endophthalmitis

Taraprasad Das

Prophylaxis of endophthalmitis with topical povidone-iodine was a single-center (the New York Eye and Ear Infirmary of Mount Sinai, New York, USA) randomized study between January 1988 and February 1990. It consisted of two phases. The phase 1 study, January 1988 to March 1989, was a retrospective study, and the phase 2 study, April 1989 to February 1990, was a prospective study [1].

Study Design (Table 34.1)

The study was conducted in two operating suites of New York Eye and Ear Infirmary of Mount Sinai. Each suite consisted of five operating rooms, located in two different floors of the infirmary. Two antiseptics were used for preoperative conjunctival preparation; they were Argyrol and 5% povidone-iodine (PI).

Argyrol is an antiseptic solution at varying strengths of mild silver protein. It is manufactured in the chemical industry to pharmaceutical grade using denatured pharmaceutical-grade protein for ophthalmic application and elemental silver to produce the silver protein molecule. It is recommended for use on mucous membranes to resolve local infections in mucous-membrane-lined organs. Historically, it has been extensively used in gonorrheal infections and in prevention of gonorrheal blindness.

Povidone-iodine (PI) is an antiseptic used for skin disinfection of patients and hands of the healthcare providers. PI came to commercial use in 1955, and it is on the World Health Organization (WHO) list of essential medicines. It has minimal toxicity but produces a powerful antimicrobial effect after 1 min of skin contact. This effect is attributed to the release of free iodine and persists for at least 1 h. It is believed that iodine penetrates the cell wall and reacts with amino acids and

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Table 34.1 Povidone-iodine prophylaxis study design

Study type	Study method	
	Suite A	Suite B
Retrospective comparative Phase 1. *n* = 10,608 Jan 1988–Mar 1989	Preoperative conjunctival topical application of Argyrol (*n* = 4547)	Preoperative conjunctival topical application of Argyrol (*n* = 6101)
Prospective comparative Phase 2. *n* = 8083 Apr 1989–Feb 1990	Preoperative conjunctival topical application of 5% povidone-iodine (*n* = 3489)	Preoperative conjunctival topical application of Argyrol (*n* = 4594)

Table 34.2 Povidone-iodine prophylaxis study results

Study type	Study method	
	Suite A	Suite B
Retrospective comparative Phase 1. *n* = 10,608	Topical Argyrol Total: 0.42% (19/4507) Culture +ve: 0.18% (8/4507) Culture −ve: 0.24% (11/4507)	Topical Argyrol Total: 0.40% (25/6101) Culture +ve: 0.16% (10/6101) Culture –ve: 0.25% (15/6101)
Prospective comparative Phase 2. *n* = 8083	Topical povidone-iodine Total: 0.11% (4/3489) Culture +ve: 0.06% (2/3489) Culture −ve: 0.06% (2/3489)	Topical Argyrol Total: 0.54% (25/4594) Culture +ve: 0.24% (11/4594) Culture –ve: 0.30% (14/4594)

nucleotides, which, ultimately, disrupt the cell's protein synthesis. It is contraindicated in people with iodine allergy and in people with hyperthyroid disease.

Results (Table 34.2)

There were 44 incidences of endophthalmitis in phase 1 study and 29 incidences of endophthalmitis in phase 2 study; culture-proven endophthalmitis occurred in 18 patients in phase 1 and in 13 patients in phase 2 study. There was statistically significant reduction of endophthalmitis with preoperative conjunctival application of 5% PI.

Recommendations

Povidone-iodine is recommended for both skin (10% solution) and conjunctival (5% solution) application. It is necessary that the contact time should be at least 1 min. Ideally, PI should dry after skin preparation and the conjunctival cul-de-sac should not be irrigated before 1-min contact time with PI solution.

Frequently Asked Questions

1. *What is the contact kill time of povidone-iodine?*
   A: The contact time varies from 10 to 900 s (15 min), but most of the microorganisms get killed in 60 s or less (Table 34.3).

2. *What is ideal povidone-iodine for ophthalmic care?*
   A: Wu et al. studied the impact of preoperative preparation protocol using different concentrations of PI in extracapsular cataract extraction (ECCE) with polymethylmethacrylate (PMMA) intraocular lens (IOL) insertion [2]. The protocols were:

   Protocol 1—skin preparation with 10% PI + conjunctival preparation with 5% PI
   Protocol 2—skin preparation with 10% PI + conjunctival preparation with no PI
   Protocol 3—skin preparation with 5% PI + conjunctival preparation with 5% PI

   The study showed that the skin around the eye prepared by 5% PI, conjunctiva not prepared by 5% PI, and patients with diabetes had a higher risk of developing endophthalmitis (Table 34.4).

Table 34.3 Povidone-iodine contact kill time [2]

Microorganism	Contact kill time in seconds
Staphylococcus	15–80
Streptococcus	15–30
Bacillus	10–30
Nocardia	60
Pseudomonas	15–900
Escherichia	30–120
Enterobacter	60
Proteus	15–180
Klebsiella	60
Aspergillus	30
Candida	10–20

Table 34.4 Risk of endophthalmitis after ECCE surgery (multivariate analysis) [2]

Risk factor	Definition	Endophthalmitis Adjusted OR (95% CI)	*p*
Skin disinfection	10% PI	1.0	0.003[a]
	5% PI	10.9 (2.3–52.6)	
Conjunctiva disinfection	5% PI	1.0	0.035[a]
	Without PI	5.6 (1.1–27.9)	
Diabetes	Absent	1.0	0.062
	Present	3.5 (0.9–13.1)	

CI confidence interval, *OR* odds ratio, *PI* povidone-iodine
[a]Statistically significant ($p < 0.05$)

3. *Once prepared, how long does the povidone-iodine solution last?*
   A: Povidone-iodine (PI) solution is susceptible to contamination with *Pseudomonas cepacia*, which could be passed on to patients [3]. Hence PI solution should be prepared fresh every day, and the remaining must be discarded at the end of the day. Fortunately, ophthalmic preparations are now available that is dispensed in small volume.

4. *What are the other preoperative endophthalmitis prophylaxis measures in cataract surgery?*
   A: Preoperative topical antibiotics, preoperative lash trimming, saline irrigation of the eye before the start of cataract surgery, and postoperative subconjunctival antibiotics are some of the commonly practiced prophylactic measures to prevent bacterial endophthalmitis. Ciulla et al. selected 88 published articles (from 329 references) for a systematic review to look for evidence-based recommendation [4]. The recommendations were ranked into two categories—clinical rating and evidence rating (Table 34.5).

   Preoperative application of PI was the only prophylactic measure that had superior rating for prevention of post cataract surgery endophthalmitis (Table 34.6).

   This systematic review was before the European Society of Cataract and Refractive Surgery (ESCRS) endophthalmitis prophylaxis study that showed reduction of endophthalmitis with use of intracameral cefuroxime [5]. The ESCRS has a strong evidence (A1) for use of intracameral cefuroxime in prevention of post cataract surgery endophthalmitis.

Table 34.5 Recommendation rating

Rating	Level	Interpretation
Clinical	A	Crucial to clinical outcome
	B	Moderately important to clinical outcome
	C	Cannot be related to clinical outcome
Evidence	I	Strong supporting evidence
	II	Substantial evidence, but some deficiencies
	III	Weak evidence

Table 34.6 Clinical recommendations and grouped evidence rating for commonly used prophylactic intervention in prevention of post cataract surgery endophthalmitis [3]

Prophylactic intervention	Clinical recommendation rating	Grouped evidence rating
Subconjunctival antibiotics	C	III
Preoperative lash trimming	C	III
Preoperative saline irrigation	C	III
Preoperative povidone-iodine antisepsis	B	II
Preoperative topical antibiotics	C	III
Irrigating solutions containing antibiotics	C	III

Table 34.7 Comparison between povidone-iodine and chlorhexidine

Properties	Povidone-iodine		Chlorhexidine	
	Activated iodine reacts by electrophilic reaction with the enzymes of the respiratory chain and with the amino acids from the cell membrane proteins both located in the bacterial cell wall. The tertiary structure necessary for maintaining the respiratory chain is destroyed, and the microorganism is irreversibly damaged		Absorbs the bacterial structure causing a disorganization of the bilayered cytoplasmic membrane. The respiratory chain is interrupted, and the membrane-bound ATPase is inhibited. At a certain concentration range, lysis of cell wall resulting in release of the interior of the cell can occur	
Microbial efficacy	Gram +ve cocci	Y	Gram +ve cocci	Y
	Gram −ve bacilli	Y	Gram –ve bacilli	Y
	Bacterial spores	Y	Bacterial spores	N
	Yeast	Y	Yeast	Y
	Fungus	Y	Fungus	Y[a]
	Virus	Y	Virus	Y
	Bacteriophages	Y	Bacteriophages	N
Applications	Skin antiseptics	Y	Skin antiseptics	Y
	Surgical hand disinfection	Y	Surgical hand disinfection	Y
	Wound cleaning	Y	Wound cleaning	Y
	Minor injury application	Y	Minor injury application	Y
	Treatment of burns	Y	Treatment of burns	N
	Treatment of ulcers	Y	Treatment of ulcers	N
	Dental and oral	Y	Dental and oral	Y
Use concentration	10% to 0.01%		4% to 0.02%	

[a]Mostly fungistatic

5. *How does povidone-iodine compare with chlorhexidine?*

A: Chlorhexidine is also an antiseptic used in healthcare. In some sense, PI is superior; the difference between the two is shown in Table 34.7.

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Chapter 35
Dexamethasone in Endophthalmitis

Taraprasad Das

Intravitreal dexamethasone on bacterial endophthalmitis was a single-centre (LV Prasad Eye Institute, Hyderabad, India) prospective randomized study between January 1993 and December 1994 [1]. This study addressed three issues connected to the use of intravitreal dexamethasone in exogenous bacterial endophthalmitis. They were (1) does it limit the ocular inflammation, (2) does it interfere with infection control action of intravitreal antibiotics and (3) does it impact the final visual recovery?

Study Design

See Table 35.1.

Table 35.1 Study design and study drugs

Study eye	Control eye
Core vitrectomy Intravitreal antibiotics[a] Intravitreal dexamethasone[b]	Core vitrectomy Intravitreal antibiotics[a]

[a]Amikacin 400 μg + vancomycin 1.0 mg, each in 0.1 ml
[b]Dexamethasone phosphate 400 μg in 0.1 ml

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Table 35.2 Inflammation scoring [1]

Tissue	Response	Points				
		0	1	2	3	4
Cornea	Clarity	Clear	Mild	Moderate (iris visible)	Severe (iris bare details)	Opaque (no iris view)
	Abscess	None	<1 mm	1–2 mm	3–4 mm	>5 mm
Anterior chamber	Flare/cells	None	Trace	Mild	Moderate	Severe
	Fibrin/hypopyon	None	Mild <25%	Moderate >25%	Severe <75%	No iris view
Iris	Blood vessels	None	Mild	Moderate	Severe	NVI
	Exudates over	None	Mild <25%	Moderate <50%	Severe <75%	Pupil occluded
Vitreous	Flare	None	Trace	Mild	Moderate	Severe
	Opacities	None	Cells	Clumps	Red reflex	Opaque

NVI new vessels iris
Additional scoring: cornea opaque, add 20; AC opaque, add 15; pupil fully covered with exudate, add 10; vitreous opaque, add 5

Inflammation Scoring (Table 35.2)

Modified from the one used by Meredith [2], this study quantified the inflammation associated with endophthalmitis. The scoring was done in a scale of 0–4 with additional allowance for poor clarity of ocular tissues. The inflammation score (IS) was based on the clinical picture of the cornea, anterior chamber, iris and vitreous.

Results

The study consisted of 63 patients, 32 postoperative and 31 posttrauma endophthalmitis; 39 patients (62%; 18 postoperative, 56.2%, and 21 posttraumatic, 67.7%) were culture-proven endophthalmitis. There was reduction of inflammation score in eyes that received intravitreal dexamethasone irrespective of culture positivity in both postoperative and posttrauma endophthalmitis. At the end of 3 months, the inflammation score was nearly similar irrespective of adjunctive intravitreal dexamethasone or no dexamethasone therapy. Intravitreal dexamethasone did not affect the final visual outcome in both postoperative and posttrauma endophthalmitis, but reduction of inflammation score was higher in eyes that received intravitreal dexamethasone (Table 35.3).

Recommendation

The study recommended the use of intravitreal dexamethasone along with intravitreal antibiotics in bacterial endophthalmitis. It is particularly recommended in situations where oral corticosteroids could not be used for medical reasons.

Table 35.3 Relative percentage change in inflammation [1]

Time period	Intravitreal antibiotics Plus intravitreal dexamethasone Inflammation score % (SD) (median)	Intravitreal antibiotics No intravitreal dexamethasone Inflammation score % (SD) (median)	*p*
1 week	19.2 (26.0) (20.0)	−18.3 (35.7) (− 23.9)[a]	0.0001[b]
4 weeks	47.5 (35.8) (56.5)	26.0 (37.7) (33.8)	0.0037[b]
3 months	85.9 (11.3) (84.2)	81.0 (16.2) (78.0)	0.1863

[a]Increase in inflammation
[b]Statistically significant

Frequently Asked Questions

1. *Is oral corticosteroid an ideal replacement for intravitreal dexamethasone?*
   A: The Endophthalmitis Vitrectomy Study (EVS) did not use intravitreal dexamethasone though; the study used oral prednisolone (1 mg/kg of body weight) for 10 days or so starting a day after the intravitreal antibiotics were injected [3]. Thus, it did not cover the inflammation immediately. Since there is a time lag between the occurrence and presentation of endophthalmitis, the patients usually present with a lot inflammation. The oral corticosteroid will take 24 h or so to reach optimal vitreous concentration. An experimental *Pseudomonas aeruginosa* endophthalmitis has shown that the beneficial effect of intravitreal dexamethasone is lost if the therapy is delayed beyond 5 h [4]. Hence an intravitreal dexamethasone (or other corticosteroids) helps reduce the inflammation effectively only when injected early. We have also shown that a more aggressive therapy with intravitreal triamcinolone helps contain intense inflammation when infection is adequately controlled [5].

2. *What are the controversies in intravitreal corticosteroid usage?*
   A: Corticosteroids are widely used in treatment of inflammatory disease. The primary value lies in minimization of inflammatory response; the arguments against their use are possible interference with infection control and decreased concentration of intravitreal antibiotics.

   Two large retrospective studies did not find any deterrent effect of intravitreal corticosteroids in post-cataract surgery acute endophthalmitis [6, 7], and one retrospective series detected worse visual outcome in adjunctive intravitreal dexamethasone [8]. Since the EVS publication, the American Society of Retina Specialists (ASRS) Preferences and Trends (PAT) survey has sought opinion on the use of corticosteroids in endophthalmitis only once, in 2004. This survey showed that 59% of the respondents use corticosteroid in post-cataract surgery endophthalmitis, either systemic and/or intravitreal—36% use intravitreal corticosteroid alone, 7% use both systemic and intravitreal corticosteroid and 16% use only systemic corticosteroid [9].

   The half-life of intravitreal dexamethasone is short. But it is known to potentiate the effect of vancomycin in experimental and clinical endophthalmitis [10, 11], and even a dose as small as 0.2 mg in vitreous cavity is useful [11]. Of all

corticosteroids, intravitreal dexamethasone is widely studied, and it is prudent to consider its usage at least in situations where oral corticosteroid is otherwise contraindicated.

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