# Endophthalmitis

Marlene L. Durand
Joan W. Miller
Lucy H. Young
*Editors*

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*Editors*
Marlene L. Durand, MD
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts
USA

Joan W. Miller, MD
Massachusetts Eye and Ear
Harvard Medical School
Boston, Massachusetts
USA

Lucy H. Young, MD, PhD
Massachusetts Eye and Ear
Harvard Medical School
Boston, Massachusetts
USA

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*With love and gratitude:*

*To my husband, Dr. Brooke Swearingen, and our daughters, Jennifer and Laura.*

Marlene L. Durand, MD

*To my husband, John B. Miller, PhD, and our children, John, Douglas, and Mary.*

Joan W. Miller, MD

*To my parents, Professor Tsen Men Young and Mrs. Pei Lan Liu.*

Lucy H. Young, MD, PhD

# Preface

Endophthalmitis is a rare but dreaded complication of common eye surgeries such as cataract surgery, intravitreal injections such as those given to treat neovascular age-related macular degeneration, penetrating eye trauma, and systemic infections such as liver abscess or endocarditis. Endophthalmitis leads to blindness in some eyes and irreversible decrease in visual acuity in most eyes. Prompt diagnosis and treatment of endophthalmitis is essential to save vision. The purpose of this textbook is to provide clinicians and researchers with a comprehensive and current resource for understanding this important eye infection. This understanding in turn may save the vision of future patients affected by endophthalmitis.

The authors of the individual chapters are experts in the field. The first chapter is a general overview of endophthalmitis and includes a discussion of the various types of endophthalmitis (e.g., post-cataract, endogenous) and the relative frequencies of each type as seen around the world. The second chapter summarizes the latest research on the pathogenesis of bacterial endophthalmitis, including a discussion of the role of bacterial virulence factors and the immune system in determining the severity of the intraocular infection. The third and fourth chapters discuss the diagnosis of endophthalmitis by microbiologic and molecular techniques. Chapter 3 describes methods used in the clinical microbiology laboratory to identify microbes including new techniques such as mass spectrometry, while Chapter 4 includes a discussion of the increasing impact of molecular techniques such as polymerase chain reaction in the rapid diagnosis of endophthalmitis. Chapters 5, 6, 7, 8, 9, 10, 11, 12, and 13 discuss in detail the major types of endophthalmitis: acute-onset postoperative (including post-cataract) endophthalmitis, chronic endophthalmitis masquerading as uveitis, endophthalmitis after intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents or corticosteroids, bleb-related endophthalmitis (i.e., related to the presence of a glaucoma filtering bleb), endophthalmitis after penetrating eye trauma, endogenous endophthalmitis (i.e., resulting from hematogenous spread of infection to the eye), exogenous fungal endophthalmitis including intraocular infections resulting from fungal keratitis, endophthalmitis related to devices such as a glaucoma drainage device or an artificial cornea (keratoprosthesis), and endophthalmitis in the immunocompro-

mised or diabetic host. The authors of these chapters include recommendations for diagnosis and treatment. Chapter 14 discusses the increasing problem of antibiotic resistance in endophthalmitis pathogens and how this affects our treatment options. Chapter 15 summarizes our current understanding of the best ways to prevent endophthalmitis. All of the chapters were written with the clinician in mind and include many helpful tables and illustrations.

We are grateful to the chapter authors for their expertise and their contributions to this textbook. We would also like to acknowledge the help of Wendy Chao, PhD, Scientific Manager, Ophthalmology Communications of Massachusetts Eye and Ear, as well as Swathiga Kathikeyan and Tanja Maihöfer of Springer International Publishing Company. Finally, we would like to thank our families for their ongoing encouragement and support.

Boston, MA, USA Marlene L. Durand, MD
Boston, MA, USA Joan W. Miller, MD
Boston, MA, USA Lucy H. Young, MD, PhD

# Contents

# Contributors

**Asaf Bar, MD** Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Neelakshi Bhagat, MD, MPH, FACS** Department of Ophthalmology, Rutgers New Jersey Medical School, Institute of Ophthalmology and Visual Science, Newark, NJ, USA

**Paulo J.M. Bispo, PhD** Department of Ophthalmology, and Department of Microbiology and Immunology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear, Boston, MA, USA

**Sandrine Boisset, PharmD, PhD** Department of Microbiology, Grenoble Alpes University, Grenoble, France

Department of Microbiology, University Hospital of Grenoble, Grenoble, France

**Michelle C. Callegan, PhD** Department of Ophthalmology, and Department of Microbiology and Immunology, University of Oklahoma College of Medicine, Oklahoma City, OK, USA

Dean A. McGee Eye Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

**Christophe Chiquet, MD, PhD** Department of Ophthalmology, Grenoble Alpes University, Grenoble, France

Department of Ophthalmology, University Hospital of Grenoble, Grenoble, France

**Pierre-Loïc Cornut, MD, PhD** Department of Ophthalmology, University of Lyon, Lyon, France

Department of Ophthalmology, University Hospital, Lyon, France

**Claes H. Dohlman, MD, PhD** Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA

**Marlene L. Durand, MD** Department of Medicine and Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Infectious Disease Service, Massachusetts Eye and Ear, Infectious Disease Unit, Massachusetts General Hospital, Boston, MA, USA

**Harry W. Flynn Jr. , MD** Department of Ophthalmology, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, Miami, FL, USA

**Rosie Gilbert, MBBS, MRCOphth** Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Michael S. Gilmore, PhD** Department of Ophthalmology, and Department of Microbiology and Immunology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear, Boston, MA, USA

**Luis J. Haddock, MD** Department of Ophthalmology, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, Miami, FL, USA

**Carol A. Kauffman, MD** Division of Infectious Diseases, Veterans Affairs Ann Arbor Healthcare System, University of Michigan Medical School, Ann Arbor, MI, USA

**Xintong Li** Rutgers New Jersey Medical School, Newark, NJ, USA

**Sue Lightman, MBBS, PhD, FRCOphth** Department of Clinical Ophthalmology, University College of London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Yingna Liu** Harvard Medical School, Boston, MA, USA

**Ann-Marie Lobo, MD** Department of Ophthalmology, University of Illinois College of Medicine at Chicago, Chicago, IL, USA

Illinois Eye and Ear Infirmary, Chicago, IL, USA

**Max Maurin, MD, PhD** Department of Microbiology, Grenoble Alpes University, Grenoble, France

Department of Microbiology, University Hospital of Grenoble, Grenoble, France

**Darlene Miller, DHSC, MPH, CIC** Department of Ophthalmology, and Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami, FL, USA

Bascom Palmer Eye Institute, Miami, FL, USA

**Joan W. Miller, MD** Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA

**John B. Miller, MD** Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA

**Kiyofumi Mochizuki, MD, PhD** Department of Ophthalmology, Gifu University Graduate School of Medicine, Gifu, Japan

**Rachael Niederer, BHB, MBChB, PhD** Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Salai Madhumathi Parkunan** Department of Microbiology and Immunology, University of Oklahoma College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

**Avni V. Patel, MD** Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear, Boston, MA, USA

**Efthymia Pavlidou, MD, MSc** Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Nidhi Relhan, MD** Department of Ophthalmology, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, Miami, FL, USA

**Akira Sawada, MD, PhD** Department of Ophthalmology, Gifu University Graduate School of Medicine, Gifu, Japan

**Stephen G. Schwartz, MD, MBA** Department of Ophthalmology, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, Miami, FL, USA

**Sophie Seguin-Greenstein, MBBS, BSc** Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Elizabeth M. Selleck, PhD** Department of Ophthalmology, and Department of Microbiology and Immunology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear, Boston, MA, USA

**Lucia Sobrin, MD, MPH** Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA

**Lazha Talat, MPH, MSc (Ophth)** Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Oren Tomkins-Netzer, MD, PhD** Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Kamyar Vaziri, MD** Department of Ophthalmology, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, Miami, FL, USA

**Malgorzata Woronkowicz, MD** Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK

**Tetsuya Yamamoto, MD, PhD** Department of Ophthalmology, Gifu University Graduate School of Medicine, Gifu, Japan

**Lucy H. Young, MD, PhD** Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA

**Marco A. Zarbin, MD, PhD** Department of Ophthalmology, Rutgers New Jersey Medical School, Institute of Ophthalmology and Visual Science, Newark, NJ, USA

# Chapter 1
# Endophthalmitis: An Overview

**Marlene L. Durand**

## 1.1 Introduction

Endophthalmitis is a potentially devastating eye infection. In most patients, endophthalmitis results in some degree of irreversible vision loss in the affected eye; in some patients, all useful vision in that eye is lost. The term "endophthalmitis" is nearly always used to describe intraocular infection due to bacteria or fungi involving the vitreous and/or aqueous. Cases of intraocular inflammation due to viruses, parasites, and noninfectious etiologies are usually classified as uveitis rather than endophthalmitis cases.

Most cases of endophthalmitis are exogenous, with infection introduced into the eye "from the outside in." The most common causes of exogenous endophthalmitis are eye surgery, intravitreal injections, and penetrating eye trauma. Patients with exogenous endophthalmitis usually develop rapidly decreasing vision and increasing eye discomfort or eye pain within days of the inciting event. Signs of systemic infection, such as fever and leukocytosis, are absent.

Endogenous endophthalmitis results from seeding of the eye during bacteremia or fungemia. Some patients present primarily with eye symptoms and without signs of systemic infection, such as patients with transient fungemia or bacteremia from intravenous drug abuse. Others, such as those with endocarditis, usually have systemic signs of infection on presentation and may even develop eye symptoms after treatment has been started for the underlying systemic infection.

Most patients with endophthalmitis have acute endophthalmitis and present within hours or a few days of the onset of eye symptoms. These patients may rapidly

M.L. Durand, MD
Department of Medicine and Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Infectious Disease Service, Massachusetts Eye and Ear, Infectious Disease Unit, Massachusetts General Hospital, Boston, MA, USA
e-mail: mdurand@mgh.harvard.edu



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lose vision without appropriate treatment and this vision loss may be permanent. Acute endophthalmitis is a medical emergency.

## 1.2 Categories of Endophthalmitis and Epidemiology

The category or type of endophthalmitis, such as postoperative, post-injection, post-traumatic, bleb-related, or endogenous, influences the clinical presentation, microbiology, and visual outcome. Visual outcome is influenced primarily by four factors: baseline vision, vision on presentation with endophthalmitis, promptness of appropriate treatment, and the microbial etiology of the endophthalmitis. Virulent organisms, such as streptococci, are associated with poor visual outcomes regardless of the category of endophthalmitis [1–5].

The relative frequency of the various types of endophthalmitis seen by ophthalmology centers worldwide varies. For over 20 years, for example, hospitals in Asia have seen many cases of endogenous endophthalmitis due to hypermucoviscous strains of *Klebsiella pneumoniae* (serotype K1 or K2) and associated with a liver abscess [6]. As a consequence, these centers typically report higher rates of endogenous endophthalmitis than do centers in the U.S. or Europe, where this infectious syndrome is still rare. Within a geographic region, the relative frequency of different categories of endophthalmitis may also vary. Ophthalmologists practicing in a large tertiary care hospital in a major city will likely see a different mix of endophthalmitis cases than will ophthalmologists practicing in a private practice clinic or in a rural area. The years reviewed in retrospective studies also influence the relative frequency of the categories of endophthalmitis reported. Few cases of post-intravitreal injection endophthalmitis are reported in studies prior to 2005, because the Food and Drug Administration approved the first anti-vascular endothelial growth factor (anti-VEGF) agent in December 2004. Prior to that, the intravitreal injections used were primarily corticosteroids, and these were given infrequently. The use of corticosteroid injections has increased over the past decade, but anti-VEGF injections are far more frequent. Anti-VEGF agents are typically given monthly so the number of injections per patient is high and the endophthalmitis risk is cumulative. Centers that perform both cataract surgery and intravitreal anti-VEGF injections have noted a change in the relative proportion of endophthalmitis cases due to injections. In a study from Israel of 80 endophthalmitis cases seen 2003–2010, the leading cause of endophthalmitis changed from postoperative to post-injection over that time period, with post-injection cases increasing from 13 to 34 % of all endophthalmitis cases between 2003–2006 and 2007–2010 [7]. A study from Australia of all 101 post-cataract and post-injection endophthalmitis cases treated in 2007–2010 reported similar findings, with post-injection cases accounting for 52 % and postoperative 48 % of endophthalmitis cases [8].

Table 1.1 lists the relative contribution of the different types of endophthalmitis to the total number of cases of endophthalmitis seen, as reported by 12 large series from 11 countries. Most of these studies reflect the experience of a single large

**Table 1.1** Major categories of endophthalmitis reported around the world, from various time periods

| Country of study origin | *N* | Study years | Postoperative[a] (%) | Post-intravitreal injection[b] (%) | Post-traumatic (%) | Endogenous (%) | Bleb-related (%) | Keratitis-related or other[c] |
|---|---|---|---|---|---|---|---|---|
| France (64 sites) [15] | 167 | 1988–1989 | 67 | 0 | 19 | 14 | 0 | 0 % |
| USA [9]* | 278 | 1996–2001 | 54 | 0 | 13 | 8 | 18 | 7 % other or unknown |
| Turkey [10]* | 80 | 2001–2006 | 75 | 0 | 16 | 0 | 5 | 4 % other |
| India [11]* | 107 | 2006–2009 | 43 | 0 | 40 | 17 | 0 | 0 % |
| Brazil [12]*[d] | 100 | 2006–2009 | 62 | N/A | 12 | 0 | N/A | 26 % N/A |
| S. Korea (8 centers, 1 region) [16] | 197 | 2004–2010 | 61 | N/A | 15 | 11 | 2 | 11 % other |
| Iran [14]* | 65 | 2006–2011 | 65 | 0 | 12 | 14 | 2 | 8 % keratitis-related |
| Egypt [13]* | 31 | N/A, before 2012 | 42 | 0 | 58 | 0 | 0 | 0 % |
| England [3]*[d] | 47 | 1999–2012 | 81 | 11 | 2 | 6 | 0 | 0 % |
| Australia (multiple centers, one region) [17] | 205 | 1998–2013 | 41 | 9 | 14 | 24 | 3 | 9 % |
| Israel [7]* | 80 | 2003–2010 | 54 | 23 | <10[e] | <14[e] | <14[e] | <14%[e] |
| Australia [8]*[f] | 101 | 2007–2010 | 48 | 52 | N/A | N/A | N/A | N/A |

*N/A* not available or not applicable

*Starred studies are series from single tertiary care hospitals located in major cities

[a]Some series report all postoperative endophthalmitis, some only post-cataract endophthalmitis

[b]Intravitreal injections are primarily of anti-VEGF agents, the first of which was approved by the Food and Drug Administration in December 2005. Corticosteroids account for a small proportion of injections

[c]"Other" includes unknown or not specified

[d]These series included only cases caused by bacteria

[e]This study included post-traumatic and unknown etiology cases (total 10 %) and endogenous, bleb-related, and keratitis-related cases (total 14 %)

[f]This study included only post-cataract and post-injection endophthalmitis cases

tertiary care hospital [3, 7–14], while three studies reflect the combined experience of several large hospitals in a single region of a country or multiple ophthalmology centers across the entire country [15–17]. Considering all of these reports, the etiologies of endophthalmitis include postoperative in 43–81 % of cases, post-injection in 0–52 %, post-traumatic in 2–58 %, endogenous in 0–24 %, bleb-related in 0–18 %, and keratitis-related or "other" in 0–26 %.

## 1.3 Pathogenesis

The ocular surface is colonized by multiple microbes, primarily ones that also colonize the skin such as coagulase-negative staphylococci. Endophthalmitis after surgery is often due to the patient's own colonizing bacteria. In the Endophthalmitis Vitrectomy Study of acute post-cataract bacterial endophthalmitis in the U.S., lid skin cultures were taken at the time the patient presented with endophthalmitis along with intraocular cultures (aqueous or vitreous). For 105 patients diagnosed with coagulase-negative staphylococcal endophthalmitis and for whom paired skin and intraocular cultures were available, these isolates were identical in 68 % [18]. In a study from Australia, surveillance cultures of the conjunctiva and aqueous were obtained in 98 patients undergoing cataract surgery [19]. While none of the surveillance aqueous cultures grew bacteria, one patient developed postoperative *Staphylococcus epidermidis* endophthalmitis, and the isolate was indistinguishable from the patient's preoperative *S. epidermidis* conjunctival isolate by pulsed-field gel electrophoresis [19].

The ocular surface and skin cannot be completely sterilized by any preoperative antibiotic or antiseptic, so a few of these colonizing microbes are introduced into the eye during surgery. Studies utilizing surveillance cultures of the aqueous during cataract surgery have reported positive cultures in as many as 31–46 % of cases [20, 21], yet endophthalmitis is very rare and occurs in less than 0.1 % of cases. This discrepancy is presumably due to the immune system's ability to clear a small burden of relatively avirulent microbes. The constant turnover of aqueous humor also helps to reduce endophthalmitis risk in anterior segment surgery. The vitreous is a gel that does not turn over, and communication with the vitreous during cataract surgery increases endophthalmitis risk by six-fold or more [22].

The normal flora of the conjunctiva resembles skin flora, and the most common resident bacteria are coagulase-negative staphylococci, *Propionibacterium* species, and *Corynebacteria* (diphtheroids). Several studies that have included conjunctival surveillance cultures reported colonization with *S. epidermidis* and other coagulase-negative staphylococci in approximately 75 % of eyes, *S. aureus* in 5–8 % (one study 20 %), viridans streptococci in 1–2 %, beta-hemolytic streptococci in 0–5 %, enterococci in 1–2 %, *Corynebacteria* in 6–8 % (one study 63 %), *Propionibacteria* in 7–30 %, *Bacillus* in 0–5 %, gram-negative bacilli (e.g., *Pseudomonas*, *Escherichia coli*, etc.) in 4–9 %, and fungi in 1 % [19, 23–26]. These studies were not from tropical climates, however, where the relative frequency of colonizing fungi may be

higher. Given the high rate of colonization of skin and conjunctiva by coagulase-negative staphylococci, it is not surprising that these bacteria cause the majority of postoperative endophthalmitis cases.

Viridans streptococci have caused a larger proportion of post-injection than post-cataract endophthalmitis cases. This increased frequency of post-injection streptococcal endophthalmitis may be due to contamination of the ocular surface by oral flora bacteria. Viridans streptococci are common members of the oral flora. Using masks or observing a strict no-talking policy has been associated with a decrease in the incidence of post-injection viridans streptococcal endophthalmitis in some studies [27]. Post-injection endophthalmitis is further discussed in Chap. 7. In post-traumatic endophthalmitis, some microbes introduced into the eye are likely from the ocular surface flora, which may account for the coagulase-negative post-traumatic cases. However, other pathogens are most likely from the environment and inoculated into the eye by the trauma. *Bacillus*, for example, is a common soil organism and an important cause of post-traumatic endophthalmitis; most of these bacteria are likely introduced during the trauma from an environmental source. Post-traumatic endophthalmitis is discussed in Chap. 9. In bleb-related endophthalmitis, the filtering bleb offers only a thin barrier to surface bacteria. When the bleb becomes colonized with a virulent species of bacteria, such as *Streptococcus pneumoniae*, blebitis or endophthalmitis may result soon afterwards. Most cases of bleb-related endophthalmitis are due to virulent bacteria. In endogenous endophthalmitis, bacteria or fungi seed the eye via the bloodstream. Bacteremia or fungemia may be transient, as often occurs during intravenous drug abuse, or more sustained, as in endocarditis or liver abscess.

A high burden of pathogens introduced into the eye may be an important factor in some cases of endophthalmitis, particularly in cases that occur in clusters or outbreaks related to surgery or intravitreal injections. Inadvertent use of a contaminated solution during a procedure can lead to a high case attack rate. Patients often develop symptoms rapidly, reflecting not only pathogen virulence but also the high inoculum. In an outbreak of post-injection endophthalmitis due to contamination of the compounded anti-VEGF agent by oral flora streptococcal species, all 12 patients developed eye symptoms 1–6 days post-injection [28]. The cause of the outbreak was traced to the compounding pharmacy that prepared the anti-VEGF agent. Outbreaks due to molds may produce an indolent endophthalmitis with delayed onset of symptoms. In an outbreak due to a single lot of triamcinolone contaminated by the mold *Bipolaris hawaiiensis*, endophthalmitis developed in 82 % of 17 eyes receiving the intravitreal injections, but onset of symptoms was delayed in most, with a median onset of 83 days post-injection [29]. In an outbreak of post-cataract *Fusarium oxysporum* endophthalmitis involving 20 patients and thought to be due to contaminated viscoelastic filling material, the onset of symptoms was similarly delayed, occurring 16–79 days postoperatively [30]. However, the burden of contaminants is presumably so high in some outbreaks that even molds may produce a rapid onset of symptoms. Seven patients involved in an outbreak of *Fusarium solani* post-cataract endophthalmitis due to contaminated intracameral cefuroxime injections developed endophthalmitis within 4 days postoperatively [31].

The pathogenesis of endophthalmitis at the cellular level is detailed in Chap. 2. A number of advances have been made in our understanding of the basic mechanisms of endophthalmitis pathogenesis. Retinal damage from endophthalmitis occurs not only from bacterial or fungal virulence factors but also from the host inflammatory reaction to those microbes. Advances in basic science regarding pathogenesis mechanisms in endophthalmitis offer hope for future therapies that address not only the invading microbe but also the inflammatory response.

## 1.4 Clinical Features

Most patients with bacterial endophthalmitis present acutely, complaining of decreasing vision over a few hours to a few days. A majority also complain of eye pain or discomfort. In the Endophthalmitis Vitrectomy Study, 75 % of patients developed symptoms within 1 week postoperatively, and these included decreased vision (95 % of patients), red eye (80 %), and eye pain (75 %) [32]. In patients with endophthalmitis due to virulent pathogens, the onset of symptoms is usually faster, inflammation greater, and presenting vision worse [33]. Compared with endophthalmitis due to coagulase-negative staphylococci, patients with endophthalmitis due to *S. aureus*, streptococci, "other" gram-positive cocci, or gram-negative bacilli were twice as likely (46 % versus 23 %) to develop symptoms within the first 2 postoperative days and twice as likely (47 % versus 24 %) to present with light perception only vision. Postoperative endophthalmitis is discussed further in Chap. 5.

Signs of systemic infection, such as fever, are absent in nearly all exogenous endophthalmitis cases and initially may be absent in endogenous cases. On examination of the eye, a hypopyon may be seen in many cases (Fig. 1.1a), and view of the fundus is often limited due to diffuse inflammation in the aqueous and/or vitreous (Fig. 1.1b). Following effective treatment with intravitreal antibiotics, and with vitrectomy in some cases as well, the inflammation gradually clears (Fig. 1.1c). Final visual acuity, however, depends on many factors and often cannot be determined for several weeks to months.

The differential diagnosis of acute postoperative endophthalmitis is a sterile inflammatory response, but features are not usually sufficiently distinct to differentiate this syndrome from endophthalmitis at the time of presentation. The fact that culture-negative endophthalmitis cases have relatively good visual outcomes may partly reflect the fact that this category may include some cases due to sterile inflammation rather than infection. As molecular diagnostic techniques improve and become more widely available, culture-negative cases are likely to be better characterized.

In contrast with bacterial endophthalmitis, many cases of fungal endophthalmitis have a subacute presentation, with days to several weeks of symptoms. Examination of the eye may reveal that the inflammation has a "clumped" appearance, with a thick white or cream-colored mass in the aqueous (Fig. 1.2) and/or "snowballs" or

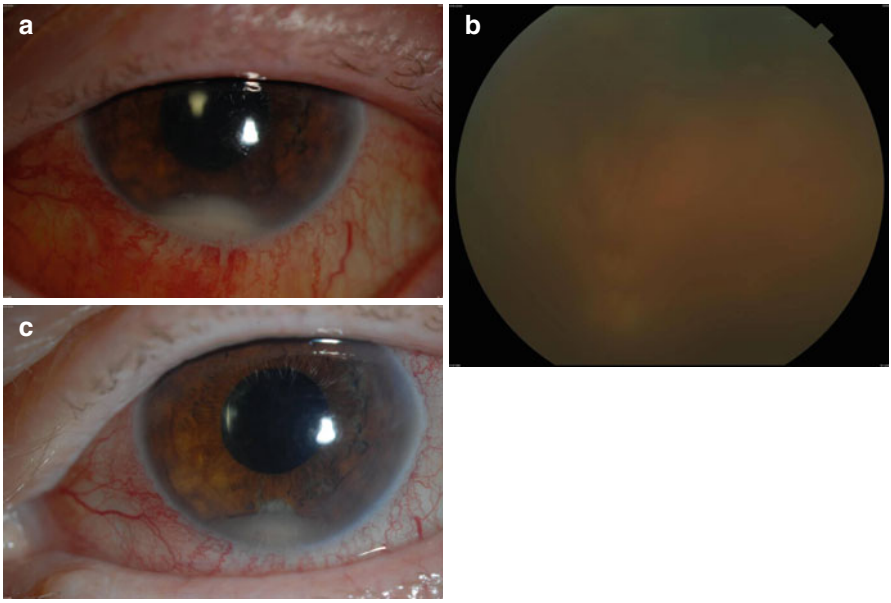


**Fig. 1.1** (**a**) Endogenous endophthalmitis in an elderly man who presented with rapid decrease in vision in one eye. On questioning, he acknowledged 3 days of chills; blood cultures were drawn and grew *Staphylococcus aureus*. A source was not found despite extensive evaluation. Photo taken after the initial intravitreal injection of antibiotics; a hypopyon is visible. (**b**) Funduscopic view in the same patient. The retina is obscured by diffuse intraocular inflammation, which is typical in acute bacterial endophthalmitis due to virulent bacteria. (**c**) Same patient, 2 days later; the hypopyon is smaller

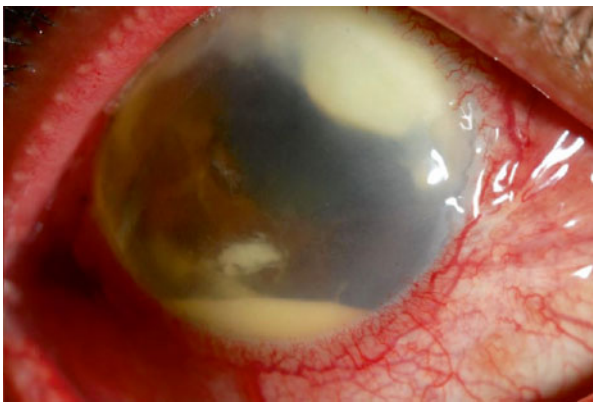

**Fig. 1.2** Exogenous mold endophthalmitis in a middle-aged patient with a glaucoma drainage device, implanted 8 years earlier. Note the thick white material in the anterior chamber; cultures of this grew *Scedosporium*. This "clumped" appearance of the intraocular inflammation is typical of mold endophthalmitis

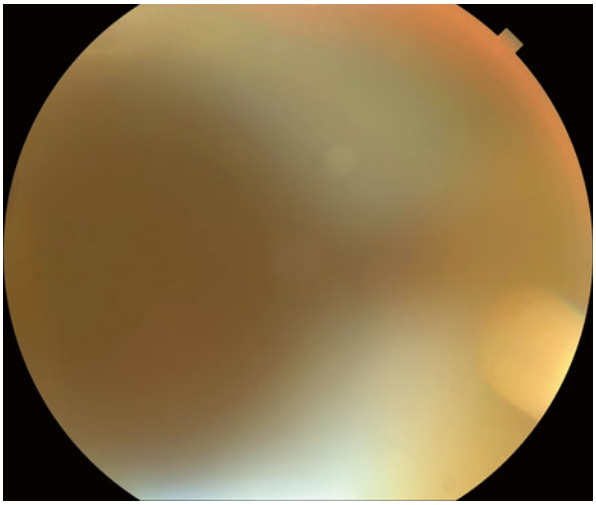

**Fig. 1.3** Occult endogenous *Candida* endophthalmitis presenting as uveitis. The patient was a middle-aged woman with multiple medical problems who had failed 1 month of empiric treatment for presumed uveitis at another facility. She had been afebrile. On presentation to Massachusetts Eye and Ear Infirmary, examination showed marked vitreous inflammation with a small white "snowball" in the superotemporal quadrant. Vitrectomy cultures grew *Candida albicans*; blood cultures and systemic evaluation were negative. The patient had been treated for pneumonia 2 months before developing eye symptoms and had had a peripherally inserted central venous catheter (PICC line) for 10 days during this treatment. Transient candidemia may occur while a temporary central venous catheter is in place and may be unrecognized or asymptomatic. If the eye was seeded at that time, a delayed onset endogenous *Candida* endophthalmitis may result

"string of pearls" in the vitreous. Rare cases of bacterial endophthalmitis due to low-virulence pathogens such as *Propionibacterium acnes*, as well as many cases of fungal endophthalmitis, have a subacute or chronic presentation. These cases may be initially misdiagnosed as uveitis (Fig. 1.3). Patients with subacute or chronic endophthalmitis typically have mild or no eye pain initially and only complain of progressive decrease in visual acuity in the involved eye.

In most series, 85–95 % of endophthalmitis cases are exogenous, with the majority of cases following eye surgery, an intravitreal injection, or penetrating trauma and presenting within a week after the event. Rare cases, usually due to an indolent organism such as *P. acnes* or a fungus, may present subacutely but with symptoms starting soon after the inciting event. These cases may be mistaken for uveitis and treated with topical corticosteroids with initial improvement but ultimately followed by worsening. Two post-cataract endophthalmitis cases have been described due to molds, for example, that were initially treated with topical corticosteroids before clinical worsening led to vitrectomy and the correct diagnosis [34]. Chronic endophthalmitis masquerading as uveitis is further discussed in Chap. 6 and exogenous fungal endophthalmitis in Chap. 11.

In contrast with acute postoperative endophthalmitis, most infections related to a filtering bleb, glaucoma drainage device, or keratoprosthesis present months to

years postoperatively, but with a rapid onset of symptoms. An antecedent surface infection (e.g., blebitis) or defect (conjunctival erosion of glaucoma drainage device tube) often precedes the endophthalmitis. Bleb-related endophthalmitis is discussed in Chap. 8 and device-related endophthalmitis in Chap. 12.

Endogenous endophthalmitis accounts for 5–15 % of all endophthalmitis cases in most series and has a different presentation when due to bacteria than fungi. In endogenous bacterial endophthalmitis, eye symptoms usually develop rapidly over 1 or more days, while in endogenous fungal endophthalmitis, symptoms often develop slowly over several days to several weeks. Endogenous fungal endophthalmitis is particularly important in organ and hematopoietic stem cell transplant recipients, in whom the eye findings may provide early clues to an occult systemic fungal infection. Endogenous endophthalmitis is further discussed in Chap. 10 and endophthalmitis in immunocompromised patients in Chap. 13.

## 1.5 Microbiology

Table 1.2 lists the most common pathogens by category of endophthalmitis, based on large series. In postoperative endophthalmitis, gram-positive bacteria cause approximately 95 % of culture-positive cases including 70 % due to coagulase-negative staphylococci [32]. The microbiology may be changing in post-cataract endophthalmitis in some locations. Some centers in Europe and Asia have reported a higher frequency of streptococcal or enterococcal isolates than previously noted in the 1995 Endophthalmitis Vitrectomy Study. Streptococci caused 9 % and enterococci 2 % of the 290 culture-positive cases in the Endophthalmitis Vitrectomy Study [35], while streptococci caused 6 of 14 culture-positive cases in the 2006 European Society of Cataract and Refractive Surgeons study [36–38] and enterococci caused 28 % of 88 culture-positive cases in a series from Sweden [22].

**Table 1.2** Categories of endophthalmitis and the most common pathogens associated with each category

| Category of endophthalmitis | Most common pathogens |
|---|---|
| Post-cataract (or postoperative) | Coagulase-negative staph |
| Post-intravitreal injection | Coagulase-negative staph, streptococci |
| Post-traumatic | Coagulase-negative staph, *Bacillus*, streptococci (also gram-negative bacilli, fungi in some areas) |
| Endogenous | *Klebsiella pneumoniae*[a], *S. aureus*, streptococci, *Candida* |
| Bleb-related | Streptococci |
| Post-keratoplasty | *Candida* |
| Keratitis-related | Molds (e.g., *Fusarium*) |

*Coagulase-negative staph* coagulase-negative staphylococci, *S. aureus Staphylococcus aureus*, *E. coli Escherichia coli*

[a]*Klebsiella pneumoniae* = common in Asia, currently rare in the USA and Europe

A study from South Korea also found a 28 % rate of enterococci in postoperative endophthalmitis cases [39]. In tropical regions, fungi often account for 10–20 % of postoperative endophthalmitis cases. Fungi caused 18 % of 170 postoperative endophthalmitis cases in a series from India [40].

In post-injection endophthalmitis, gram-positive cocci cause approximately 95 % of cases, and both coagulase-negative staphylococci and viridans streptococci are major pathogens. In post-traumatic endophthalmitis, coagulase-negative staphylococci and *Bacillus* species are major pathogens, with *Bacillus* species causing a fulminant infection with poor visual outcome. Other pathogens include gram-negative bacilli and fungi. In bleb-related endophthalmitis, streptococci are the primary pathogens, causing approximately one-third to one-half of cases in most series [41, 42]. Other pathogens are coagulase-negative staphylococci, *S. aureus*, enterococci, and *Haemophilus influenzae*. In cases of keratitis that progress to endophthalmitis, fungi caused approximately 75 % of cases reported from southern Florida [43], but streptococci and *Pseudomonas* each accounted for 30 % of keratitis-related endophthalmitis cases in a series from Australia [44].

In endogenous bacterial endophthalmitis, *Klebsiella pneumoniae* is the major pathogen in series from Taiwan, Singapore, and other East Asian nations. In these countries, *Klebsiella* accounts for 60 % of endogenous endophthalmitis cases [45]. Most affected patients are older, diabetic, and have a *Klebsiella* liver abscess in addition to endophthalmitis; over 20 % have bilateral eye involvement [46]. In Western nations, this infectious syndrome is rare. In a study of 19 cases of endogenous bacterial endophthalmitis treated at a London teaching hospital in 1984–2001, 47 % were due to streptococci (*S. pneumoniae*, Group A or B streptococci, *S. milleri*), 21 % *E. coli*, 11 % *S. aureus*, and the remainder caused by other virulent pathogens [47]. Only one case was due to *Klebsiella*, and that case was associated with a liver abscess. Patients with the syndrome of *Klebsiella pneumoniae* liver abscess and endophthalmitis have been seen recently elsewhere in Europe and in the USA, suggesting global spread of the pathogen [48, 49].

An increasing number of multidrug resistant pathogens have been reported to cause endophthalmitis. Most of these resistant pathogens have occurred in surgery-associated outbreaks of endophthalmitis [50, 51], but some have occurred outside the outbreak setting. A center in New York, for example, reported that 18 % of the 33 culture-positive postoperative endophthalmitis cases referred in the preceding 3 years were due to methicillin-resistant *S. aureus* (MRSA) [52]. The increasing role of resistance in endophthalmitis pathogens is discussed further in Chap. 14.

## 1.6 Diagnosis

Endophthalmitis is usually diagnosed clinically and confirmed by cultures of the vitreous and/or aqueous (or blood cultures in endogenous cases). Negative intraocular cultures do not exclude a diagnosis, however. Most endophthalmitis series report that 30 % of cases have negative cultures, although some of these may

be positive by molecular diagnostic methods. Endophthalmitis is usually rapidly diagnosed and treated in cases that occur soon after eye surgery, intravitreal injections, or eye trauma. However, there may be delays in diagnosis in endogenous endophthalmitis, particularly when outpatients present to the ophthalmologist with eye symptoms but without systemic symptoms or known risk factors. One-half to two-thirds of patients with endogenous endophthalmitis present first to the ophthalmologist. The absence of systemic symptoms is particularly common in patients with endogenous fungal endophthalmitis. Ophthalmologists should ask any patient presenting with an eye examination potentially consistent with fungal endophthalmitis about risk factors such as recent hospitalizations, recent indwelling central venous catheters, or intravenous drug abuse. In endogenous bacterial endophthalmitis, systemic symptoms are present on initial evaluation approximately 80 % of the time. The absence of these symptoms can lead to a delay in diagnosis. In a review of 267 endogenous bacterial endophthalmitis cases reported in the literature, 18 % of patients had no systemic symptoms at presentation and 22 % were initially misdiagnosed, most often as uveitis, causing an average delay in diagnosis of 9.5 days [47].

In exogenous endophthalmitis, the highest yield of positive cultures is usually from vitrectomy cultures, while the next highest yield is from vitreous then aqueous aspirates. In cases in which inflammation mainly involves the aqueous (e.g., some fungal endophthalmitis cases that are keratitis-related or due to glaucoma drainage devices), aqueous cultures may have the highest yield. Blood cultures are negative in exogenous endophthalmitis but should always be obtained in suspected endogenous endophthalmitis cases.

Increasingly, molecular methods of diagnosis are being applied to intraocular samples, particularly in culture-negative cases. These methods are mainly used in research laboratories, but commercial assays should be available in the near future. Chapter 3 discusses the microbiologic methods, and Chap. 4 the molecular methods for diagnosing endophthalmitis.

## 1.7 Treatment and Visual Outcomes

Treatment of endophthalmitis is discussed in more detail for each category of endophthalmitis in Chaps. 5, 6, 7, 8, 9, 10, 11, 12, and 13. It has been known for several decades that the most important component of treatment is the intravitreal injection of antibiotics. Vitrectomy is also important in some cases, as discussed below. Cases of suspected bacterial endophthalmitis are usually treated empirically with intravitreal vancomycin plus ceftazidime. Subsequent antibiotic injections may be necessary after 48 h depending on clinical response, and the choice of these injections should be tailored to culture results. Cases of fungal endophthalmitis are treated with intravitreal amphotericin or voriconazole in addition to a systemic azole such as voriconazole for molds (e.g., *Aspergillus* or *Fusarium*) and fluconazole for *Candida* (for fluconazole-susceptible species).

All patients with endogenous endophthalmitis, bacterial or fungal, require treatment with systemic therapy for their underlying systemic infection. The role of adjunctive systemic antibiotic therapy for exogenous bacterial endophthalmitis is unknown. The Endophthalmitis Vitrectomy Study concluded that systemic antibiotics did not add any benefit to intravitreal antibiotics in treating post-cataract endophthalmitis. However, intravenous amikacin and ceftazidime were the antibiotics chosen in the study, and these have very poor activity against staphylococci, the etiology of 80 % of culture-positive cases [32]. Systemic amikacin also does not produce therapeutic intraocular levels. Because of these issues, some centers have questioned the results of the Endophthalmitis Vitrectomy Study regarding the lack of value of adjunctive systemic antibiotics [53]. Oral antibiotics such as quinolones have been used as adjunctive therapy for endophthalmitis in some centers in Europe and Australia [53, 54]. In theory, systemic antibiotics that produce therapeutic levels in the vitreous might be beneficial by prolonging the intravitreal antibiotic level achieved after the initial antibiotic injection. Most injected intravitreal antibiotics are cleared in 24–48 h. Moxifloxacin produced relatively high intraocular levels in the vitreous after oral administration in one study, exceeding the levels needed to treat a wide variety of bacteria [55]. Oral antibiotics appeared to offer some benefit as adjunctive therapy for post-cataract endophthalmitis in a retrospective study from Australia [54], and the use of oral moxifloxacin similarly appeared to be beneficial in a retrospective study from London [56]. It is not possible to draw definitive conclusions from retrospective studies, but it may be reasonable to add an agent such as moxifloxacin when initially treating bleb-related endophthalmitis cases, for example, or other cases likely to be caused by virulent pathogens such as streptococci. It should be emphasized that systemic antibiotics alone are ineffective in treating bacterial endophthalmitis, and all cases require intravitreal antibiotics.

Vitrectomy in addition to intravitreal antibiotics is beneficial in treating some cases of endophthalmitis. In the Endophthalmitis Vitrectomy Study, all patients received intravitreal antibiotics, but half were randomized to first receive emergency vitrectomy, while the other half first received needle aspirate or vitreous “biopsy” in the operating room (tap/biopsy group). Patients who presented with light perception only had better visual outcomes with vitrectomy: severe vision loss occurred in only 20 % of the vitrectomy group versus 47 % of the tap/biopsy group [32]. Vitrectomy plus intravitreal antibiotics may sterilize the eye more quickly than intravitreal antibiotics alone. Approximately 10 % of patients (13 % of tap/biopsy group, 8 % of vitrectomy group) required a second procedure during the first week, usually for ongoing inflammation, and vitreous cultures were repeated. These repeat vitreous cultures were persistently positive in 71 % of the tap/biopsy group but only 13 % of the vitrectomy group [57]. Whether initial vitrectomy would be beneficial in some endophthalmitis patients presenting with better than light perception vision has been questioned. The tap/biopsy arm of the Endophthalmitis Vitrectomy Study was not homogenous: the initial procedure in two-thirds of the tap/biopsy group was a vitreous biopsy performed with a vitrector in the operating room rather than a needle aspirate, although the latter is the more common technique used when performing “tap and inject” [57].

Visual outcomes are highly dependent on the virulence of the pathogen in addition to the promptness of appropriate therapy. Endophthalmitis cases due to relatively avirulent pathogens have a good chance of visual recovery, while cases caused by virulent pathogens do not. In the Endophthalmitis Vitrectomy Study, over 80 % of eyes with post-cataract endophthalmitis due to coagulase-negative staphylococci did reasonably well, achieving at least 20/100 vision at follow-up (only 4 % suffered severe vision loss) [32]. Patients with culture-negative endophthalmitis had similarly good results. In contrast, patients with endophthalmitis due to other pathogens fared worse: only 56 % of patients with endophthalmitis due to gram-negative bacilli, 50 % due to *S. aureus*, and 30 % due to streptococci achieved 20/100 vision or better. Large prospective studies are not available for other categories of endophthalmitis, but retrospective studies have demonstrated similar findings, with virulent pathogens producing poor visual outcomes in general. A major eye center in Florida has reviewed visual outcomes according to pathogen rather than endophthalmitis category for several highly virulent bacterial species. Final visual acuity was less than 20/400 (or ≤20/400, depending on the study) in 75 % of 63 streptococcal cases [1], 93 % of 14 enterococcal cases [58], 64 % of 22 *Bacillus* cases [59], 69 % of 16 *H. influenzae* cases [60], 70 % of 10 *Serratia* cases [61], and 92 % of 12 *Pseudomonas* cases [62]. These studies reflect cases seen over a 10-year or longer time period and at a tertiary eye hospital, where the most severe endophthalmitis cases are likely to be referred. Regardless of the pathogen, however, it is possible to achieve a good outcome in some eyes. In the series of *Bacillus* endophthalmitis noted above, 18 % of cases achieved a final visual acuity of 20/60 or better [59].

## 1.8 Conclusion

Endophthalmitis is a rare but serious infection. Ideally it should be prevented, and methods of prevention are discussed in Chap. 15. Visual outcome partly depends on the virulence of the pathogen but also on the promptness of effective therapy. Current research offers hope for finding new diagnostic techniques and new therapeutic strategies

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# Chapter 2
# The Pathogenesis of Bacterial Endophthalmitis

**Salai Madhumathi Parkunan and Michelle C. Callegan**

## 2.1 Introduction

Bacterial endophthalmitis is an infection of the eye resulting from the introduction of bacteria into the anterior and/or posterior segments following a surgical procedure (postoperative), traumatic penetrating injury (post-traumatic), or hematogenous spread (endogenous). Postoperative endophthalmitis typically results from contamination with the normal microbiota of the conjunctiva, eyelid, and skin, with coagulase-negative staphylococci being the most common cause [1–3]. The World Health Organization estimates that greater than 32 million cataract surgeries will be performed worldwide each year by 2020 [4]. Endophthalmitis is a feared complication of cataract surgery, with an incidence of 0.01–0.3 % [3, 5–7]. Approximately 2.4 million intravitreal injections were performed to treat neovascular eye disease and intraocular inflammation in 2012 [8]. The increase in the number of intravitreal injections has led to an increase in cases of injection-related endophthalmitis [9], with incidences ranging from 0.006 to 0.16 % per injection [10–12]. In the U.S., approximately two million eye injuries occur per year, and more than 40,000 cases result in permanent visual impairment [13, 14]. The incidence of post-traumatic endophthalmitis ranges from 0.9 to 17 % [15–17], and common bacterial pathogens are staphylococci and *Bacillus cereus* [15–18]. Endogenous endophthalmitis cases are relatively rare, comprising approximately 5 % of all endophthalmitis cases. The danger of endogenous endophthalmitis lies in its potential for bilateral blindness. Endogenous bacterial endophthalmitis is most often caused by *Staphylococcus*

S.M. Parkunan
Department of Microbiology and Immunology, University of Oklahoma College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

M.C. Callegan, PhD (✉)
Department of Ophthalmology, and Department of Microbiology and Immunology, University of Oklahoma College of Medicine, Oklahoma City, OK, USA

Dean A. McGee Eye Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
e-mail: michelle-callegan@ouhsc.edu



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*aureus*, streptococcal species, and gram-negative bacteria such as *Klebsiella pneumoniae* [19, 20]. Postoperative endophthalmitis is discussed in Chap. 5, post-injection endophthalmitis in Chap. 7, post-traumatic endophthalmitis in Chap. 9, and endogenous endophthalmitis in Chap. 10.

The visual prognosis after bacterial infection varies depending upon the virulence of the infecting organism, the visual acuity at presentation, and the treatment effectiveness [21]. Endophthalmitis severity can range from a mild ocular inflammation to devastating blindness and loss of the eye. In severe cases, virulent bacteria incite inflammation which, in concert with toxin production by the offending organism, results in retinal tissue damage and vision loss. Current therapies focus on sterilization and anti-inflammation, but these strategies are not always successful. Our objective in this chapter is to discuss current knowledge regarding the bacterial and host factors which contribute to the pathogenesis of endophthalmitis, in order to identify important factors which may be future targets of effective therapeutic strategies.

## 2.2 Pathogens and Virulence Factors

Bacterial pathogens, whether causing an infection of the eye or a different tissue, often synthesize one or more factors which damage tissue or interfere with the host's ability to combat the infection. The bacterial outer envelope can also be thought of as a determinant of virulence. A recent report on microbial causes of all types of endophthalmitis over a 25-year period indicated that overall, 85.1 % of isolates were due to gram-positive bacteria, 10.3 % were due to gram-negative bacteria, and 4.6 % were due to fungi [22]. Among the common bacterial pathogens were *S. epidermidis* (30.3 %) and other coagulase-negative staphylococci (9.1 %), viridans group streptococci (12.1 %), *S. aureus* (11.1 %), *Enterobacteriaceae* (3.4 %), and *Pseudomonas aeruginosa* (2.5 %) [22]. These bacterial species vary widely in their ability to infect the eye and are also unique in their intraocular behavior, inflammation potential, and virulence characteristics, which are summarized in Table 2.1.

### *2.2.1 Bacillus*

*Bacillus* is a major cause of post-traumatic endophthalmitis and may rarely cause endogenous endophthalmitis. Most cases of *Bacillus* endophthalmitis have a rapidly progressive course resulting in blindness in the involved eye within 2–3 days [23–26]. *Bacillus cereus* is the most common *Bacillus* species isolated from blinding cases of endophthalmitis. The hallmarks of *B. cereus* endophthalmitis include eye pain and rapidly developing intraocular inflammation and loss of visual acuity. Although *B. thuringiensis* is rarely regarded as a human pathogen, this species is

**Table 2.1** Virulence factors in experimental bacterial endophthalmitis

| Bacteria | Virulence factors | References |
|---|---|---|
| *Bacillus cereus* | Hemolysin BL | [36–38] |
| | PI-PLC and PC-PLC | [38, 39] |
| | Quorum sensing (PlcR) | [41, 42] |
| | Motility and swarming | [43, 45, 46] |
| | Cell wall | [43] |
| *Enterococcus faecalis* | Cytolysin | [69] |
| | Gelatinase and serine protease | [71] |
| | Quorum sensing (Fsr) | [71, 75] |
| | Aggregation substance | [78] |
| | Cell wall | [43] |
| *Staphylococcus aureus* | α-, β-, and γ- toxins | [146] |
| | Quorum sensing (Agr and Sar) | [110, 111, 145] |
| | Cell wall | [43] |
| *Streptococcus pneumoniae* | Pneumolysin | [159, 160] |
| | Autolysin | [160] |
| | Capsule | [44] |
| *Klebsiella pneumoniae* | Hypermucoviscosity | [173] |
| | MagA | [174] |
| | Cell wall | [173] |

phenotypically and genetically similar to *B. cereus* and has been isolated from cases of endophthalmitis [27]. Other *Bacillus* species such as *B. subtilis*, *B. circulans*, *B. mycoides*, and *B. licheniformis* have been isolated from cases of endophthalmitis, but are less virulent species and may be able to be treated successfully [27–31].

*Bacillus cereus* produces membrane-damaging toxins such as hemolysin BL, phosphatidylinositol-specific phospholipase C (PI-PLC), sphingomyelinase, phosphatidylcholine-specific phospholipase C (PC-PLC), and others [32–35]. Indeed, phenotypic and genotypic analysis of *Bacillus* ocular isolates identified these toxins in most strains [27]. Hemolysin BL, a pore-forming toxin, has been analyzed for its contribution to intraocular virulence. Purified hemolysin BL and crude *B. cereus* supernatants caused intraocular inflammation similar in severity to endophthalmitis [36]. However, when an isogenic mutant of *B. cereus* lacking hemolysin BL was tested in an experimental rabbit endophthalmitis model, the absence of hemolysin BL alone did not attenuate virulence [37]. Commercially available PI-PLC and PC-PLC and purified hemolysin BL, sphingomyelinase, and cereolysin O were tested for in vitro toxicity of retinal buttons, and hemolysin BL and PC-PLC were the most toxic [38]. However, analysis of the virulence of PC-PLC and PI-PLC isogenic mutants in a similar model suggested that the absence of these toxins did not significantly attenuate virulence [39]. Taken together, these studies suggested that individual *B. cereus* toxins may not be responsible for overall endophthalmitis pathogenesis.

The *B. cereus* taxonomic group harbors the quorum sensing-dependent transcriptional regulator PlcR, which controls the expression of extracellular virulence factors [40]. PlcR-regulated degradative enzymes, cell surface components, and secreted toxins are considered to be potential virulence factors [40]. PlcR-deficient *B. cereus* and *B. thuringiensis* were tested in an experimental rabbit endophthalmitis model [41]. Severe intraocular inflammation and retinal function loss (as measured by electroretinography) were observed by 12-h post-infection in eyes infected with wild-type *Bacillus*. In eyes infected with PlcR-deficient *Bacillus*, severe inflammation and retinal function loss did not occur until 30-h post-infection. These results suggested that PlcR-regulated virulence factors contributed to rapidly evolving *Bacillus* infection and other factors not regulated by PlcR contributed to endophthalmitis which evolved more slowly [41]. In addition, *B. cereus* infection-related permeability of the blood-retinal barrier occurred with the loss of the tight junction proteins zonula occludens (ZO)-1 and occludin and tight junction collapse that was not dependent on PlcR-regulated toxin production [42]. Taken together, these studies suggest that targeting the global regulation of extracellular virulence factors may be a better strategy than targeting individual toxins in attempts to attenuate *B. cereus* virulence in the eye.

The rapid intraocular growth of *B. cereus* can also be thought of as a virulence determinant. *B. cereus* replicates in mouse and rabbit eyes faster than other gram-positive endophthalmitis pathogens [43, 44]. As *B. cereus* replicates, the mass of cell walls containing predominantly peptidoglycan significantly increases, providing a rapidly proliferating innate immune stimulus. The cell wall of *B. cereus* is highly inflammogenic in the eye. Both metabolically inactive bacilli and cell wall sacculi caused significant intraocular inflammation in rabbits, but retinal function was unchanged. These results suggested that the *Bacillus* outer envelope contributed to significant intraocular inflammation during infection [43].

The ability of *B. cereus* to physically move from the initial infection site into other tissues of the eye is also a virulence determinant. Motile *B. cereus* was significantly more virulent than nonmotile *B. cereus*, as minimal inflammation occurred in eyes infected with a nonmotile *B. cereus* mutant [45]. Although the swarming capacity of *B. cereus* did not significantly contribute to pathogenesis, a deficiency in swarming did not permit migration into the anterior segment, leading to less severe inflammation [46]. To our knowledge, *B. cereus* is the only gram-positive ocular pathogen shown to actively migrate within the eye. Motility, in addition to its rapid intraocular growth and synthesis of multiple toxins, likely contributes to its enhanced virulence when compared to other gram-positive ocular pathogens.

### *2.2.2 Enterococcus*

Enterococci are commensal organisms of the gut, but are also rare causes of postoperative endophthalmitis (<5 % of post-cataract endophthalmitis cases) and more common causes of bleb-related endophthalmitis (approximately 10 % of

culture-positive cases) [47–49B]. Enterococci cause severe intraocular infections that can lead to a poor visual outcome. *Enterococcus faecalis* causes the vast majority of enterococcal endophthalmitis cases. *Enterococcus* infections, including those of the eye, can often be refractory to treatment because of antibiotic resistance [50–54].

The major virulence factors of *E. faecalis* associated with wound infections, urinary tract infections, and endocarditis include cytolysin [55–59], aggregation substance [60–62], surface carbohydrates [63], and the biofilm-associated surface protein *e*nterococcal *s*urface *p*rotein (Esp) [64]. Cytolysin is a plasmid-encoded secreted toxin that can lyse both eukaryotic and bacterial cells [55–59, 65–68]. The cytolysin operon encodes the large and small subunits of the cytolysin, $CylL_L$ and $CylL_S$, which are ribosomally synthesized in the cell and modified post-translationally by CylM. These modified peptides are then proteolytically cleaved and secreted by CylB and then activated extracellularly by CylA. Both $CylL_L$ and $CylL_S$ are required for lysis [68]. Cytolysin is the major virulence factor contributing to *E. faecalis* endophthalmitis [69]. Genomic DNA fingerprint analysis of *E. faecalis* endophthalmitis clinical isolates identified *cylA* in 46.4 % of the isolates, associating this toxin with the disease [70]. In experimental infections, rabbit eyes infected with cytolytic *E. faecalis* rapidly lost retinal architecture, while infection with non-cytolytic *E. faecalis* resulted in little to no damage to intraocular structures. Cytolytic *E. faecalis* caused a 99 % reduction in retinal function by day 3 postinfection, while an isogenic non-cytolytic *E. faecalis* strain caused a 74 % reduction [69]. Retinal function loss caused by the non-cytolytic *E. faecalis* strain may have been due to other toxic factors synthesized by this organism in the eye. *E. faecalis* mutants with deletions in gelatinase (*gelE*), serine protease (*sprE*), or both genes were tested, and the *gelE*/*sprE* double mutant caused a significantly attenuated infection course compared to the single mutants. These results suggested that *E. faecalis* gelatinase and serine protease jointly contributed to endophthalmitis pathogenesis [71].

The well-characterized Fsr quorum sensing system in *E. faecalis* regulates the expression of gelatinase and serine protease [72]. Three genes characterized in the Fsr regulatory locus include *fsrA*, *fsrB*, and *fsrC*; *fsrB* is the regulatory component in this system [72–74]. Analysis of the role of Fsr in a rabbit model of endophthalmitis indicated that a deletion of *fsrB* significantly attenuated intraocular virulence [75]. Although strategies to target *E. faecalis* quorum sensing may reduce virulence, these would not affect synthesis of the cytolysin, since this toxin is not regulated by the Fsr quorum sensing system.

The *E. faecalis* cell wall can cause intraocular inflammation. Metabolically inactive *E. faecalis* or cell wall sacculi intravitreally injected into the rabbit eyes [43] caused slight but significant reductions in retinal function at 24 h, function which returned to normal by 48-h postinfection. However, both metabolically inactive *E. faecalis* and cell wall sacculi induced the influx of neutrophils into the eye, suggesting that cell surface components contribute to the inflammatory response during endophthalmitis. Aggregation substance is a surface-bound adhesin that mediates enterococcal clumping [76]. Aggregation substance aids in bacterial adherence and

internalization into host cells, contributing to virulence in several disease models [60, 61, 63, 77]. In experimental endophthalmitis, however, aggregation substance does not appear to affect the intraocular localization of *E. faecalis* or the overall infection course [78]. The role of the biofilm-associated enterococcal surface protein, Esp, in endophthalmitis has not been evaluated.

### *2.2.3 Staphylococcus*

Staphylococcal species are the predominant bacterial agents of endophthalmitis. *Staphylococcus epidermidis* and *S. aureus* are the major staphylococcal species recovered from postoperative and posttraumatic endophthalmitis patients. *Staphylococcus aureus* is also one of the most common bacterial species isolated from endogenous bacterial endophthalmitis cases. Increased resistance of staphylococci to a number of frequently used antibiotics jeopardizes successful treatment of staphylococcal endophthalmitis [79–81].

#### 2.2.3.1 Coagulase-Negative Staphylococci

Cataracts were responsible for approximately 51 % of blindness worldwide in 2010 [82]. A recent Centers for Disease Control report estimated that 17.2 % of Americans over 40 years of age have a cataract in one or both eyes [83]. Approximately 22 million cataract surgeries are performed worldwide each year, making this one of the most common types of surgery [84]. One of the successful approaches to improving vision in cataract surgeries is intraocular lens (IOL) implantation. Cultures of the aqueous at the end of uncomplicated cataract surgery are often positive, although this contamination very rarely results in endophthalmitis. It is possible that IOLs are contaminated during surgery as well, leading to endophthalmitis in some cases [85, 86]. Coagulase-negative staphylococci are the most commonly isolated bacteria in cases of postoperative endophthalmitis [22, 87–89]. Among this group of organisms, *S. epidermidis* constitutes approximately 82 % of endophthalmitis isolates, while *S. lugdunensis* accounts for 6 % [87]. *Staphylococcus epidermidis* is a normal inhabitant of the skin and mucosa, with minimal potential to overtly cause tissue damage. *Staphylococcus epidermidis* and other coagulase-negative staphylococci do not harbor the classical membrane-damaging toxins found in *S. aureus*, but some strains of *S. epidermidis* may be beta-hemolytic.

Although *S. epidermidis* produces few if any toxins, this bacterium evades host immunity and circumvents antibiotic activities by forming biofilms [90, 91]. This trait makes *S. epidermidis* a formidable nosocomial pathogen due to its ability to colonize medical devices and implants. *S. epidermidis* can form biofilms on IOLs, in the anterior chamber, and on other intraocular surfaces [90, 92–94]. These massive microbial communities adhere to one another and to surfaces via the

production of polysaccharides and adhesive proteins in an extracellular matrix [92, 95]. Cell-to-cell contact in *S. epidermidis* biofilms is mediated by the polysaccharide intercellular adhesin encoded by the *ica* locus [96–98]. Polysaccharide intercellular adhesin contributes significantly to biofilm formation and immune evasion of *S. epidermidis* [96, 99]. The presence of the *ica* locus in biofilms from catheters and other indwelling devices [100] suggests the potential of polysaccharide intercellular adhesion to contribute to pathogenesis of *S. epidermidis* biofilms in the eye. However, one study reported that although ocular *S. epidermidis* infection isolates primarily displayed the *icaA*/*icaD* genotype, these strains were capable of forming biofilms consisting of carbohydrates, protein, and extracellular DNA [101]. Biofilm formation is facilitated by other factors such as autolysin, a surface-associated protein that mediates attachment and binds to vitronectin, and adhesive proteins clumping factor and serine-aspartate repeat protein G that mediate binding to fibrinogen [102–105]. The roles of these adhesins in endophthalmitis have not been examined.

One of the *S. epidermidis* quorum sensing systems is encoded by the *a*ccessory *g*ene *r*egulator (Agr) operon [106]. Expression of Agr in *S. epidermidis* limits biofilm formation but does not regulate polysaccharide intercellular adhesion expression [107]. Similar to the Agr system, the LuxS system in *S. epidermidis* also limits biofilm formation; its absence attenuated virulence in a device-associated infection model [108]. Neither of these quorum sensing systems has been analyzed in the context of endophthalmitis.

Unlike the situation in human eyes, rabbit eyes can spontaneously clear cases of endophthalmitis due to *S. epidermidis*. In a rabbit experimental model, endophthalmitis initiated with 5000–10,000 *S. epidermidis* resulted in inflammation more severe than that caused by injection of 170 organisms. *Staphylococcus epidermidis* organisms grew rapidly in the eye during the first 12 h, but were cleared spontaneously after 3 days [109]. Even with the high inoculum, inflammation gradually decreased in most rabbits, and only a few rabbit eyes had severe clinical inflammation [109]. This is in stark contrast with *S. aureus* endophthalmitis in rabbits, in which injection of as few as 100 *S. aureus* led to massive infiltration of inflammatory cells into the eye and almost total loss of retinal function within 3 days [110, 111]. In vitro models of *S. epidermidis* biofilms are typically used to study bacterial interactions within the biofilm [111]. Although current experimental staphylococcal endophthalmitis models involve direct injection of planktonic bacteria into the aqueous or vitreous humor [112–114], these models may be helpful in testing the virulence of biofilms grown on IOLs or other materials.

*Staphylococcus lugdunensis* is a coagulase-negative staphylococcus that is known for causing serious infections in humans that resemble those of *S. aureus*. The few reported cases of *S. lugdunensis* endophthalmitis presented with severe visual loss and dense vitritis [115]. The pathogenic mechanisms of endophthalmitis caused by *S. lugdunensis* and other coagulase-negative staphylococci remain unexplored.

#### 2.2.3.2 *Staphylococcus aureus*

*Staphylococcus aureus* is one of the most prevalent and destructive bacterial causes of endophthalmitis. The clinical outcome following *S. aureus* infection can be very poor, with reported visual acuities of 20/400 or worse [116–120]. In recent years, there has been an increase in methicillin-resistant *S. aureus* (MRSA) infections and the emergence of rare cases of vancomycin-resistant *S. aureus* (VRSA) infections. In ocular infections, the increased incidence of MRSA is a danger because MRSA strains are often resistant to multiple antibiotics including fourth-generation fluoroquinolones [120–123] and may be more virulent [124] than methicillin-sensitive *S. aureus*. Endophthalmitis caused by VRSA has been reported [125, 126].

*Staphylococcus aureus* has a vast repertoire of virulence factors which are important in ocular and non-ocular infections. These virulence factors include cell surface proteins, adhesins, immune-modulating proteins, and secreted toxins which facilitate invasion into host tissue, immune evasion, host tissue damage, and antimicrobial resistance [127, 128]. *Staphylococcus aureus* virulence factor expression is controlled by quorum sensing regulatory systems such as Agr (accessory gene regulator, described above), SarA, Sae, and Arl [129–143]. The Agr system regulates the production of a number of secreted toxins, including toxic shock syndrome toxin, α-toxin, and other hemolysins and enterotoxins. The Agr system also indirectly regulates virulence factor production through its interaction with other regulators [132–135]. The SarA system regulates virulence expression in conjunction with Agr [136]. SarA promotes the synthesis of fibronectin- and fibrinogen-binding adhesins and synthesis of α-, β-, and δ-toxins involved in cytolysis and spread of infection [137, 138]. Moreover, Agr and SarA regulate the transition from planktonic to biofilm growth. The loss of Agr strongly augments *S. aureus* attachment to polystyrene surfaces and an increased propensity to form biofilms [139], while the loss of SarA results in reduced biofilm formation [140]. SaeR/S is another regulator of virulence factors which is vital for survival during neutrophil phagocytosis [141, 142]. The Arl regulatory system also downregulates the production of protein A, but has only a minor effect on synthesis of other virulence factors like α-toxin, β-toxin, lipase, serine protease, and coagulase [130].

The importance of the Sar and Agr regulatory systems has been studied in the context of endophthalmitis. Agr-deficient *S. aureus* do not express α-toxin and express low levels of β-toxin, enterotoxin C, fibrinolysin, serine protease, and nuclease and elevated levels of coagulase, protein A, and adhesins [132, 133, 137, 144]. In an experimental endophthalmitis model in rabbits, wild-type *S. aureus* caused focal retinal damage and vitritis as early as 36-h postinfection, while eyes infected with Agr-deficient *S. aureus* had significantly less vitritis and retinal damage. These results suggest that extracellular toxins regulated by Agr contribute to the severity of *S. aureus* endophthalmitis in rabbits [110]. In contrast, experimental endophthalmitis with a SarA-deficient mutant was as virulent as infection caused by the isogenic parent strain, suggesting that toxin regulation by SarA alone was not as critical to intraocular virulence of *S. aureus* as was Agr [111]. Mutations in both the *sar* and *agr* loci led to almost complete attenuation of intraocular virulence [111]. Similarly,

mutations in the *sar* and *agr* loci reduced the severity of *S. aureus* endophthalmitis in rats [145]. As mentioned above, the importance of global regulation of toxin production in *B. cereus*, *E. faecalis*, and *S. aureus* endophthalmitis highlights an opportunity for the testing of quorum sensing inhibition in reducing the virulence of these infections.

The role of individual toxins in the pathogenicity of *S. aureus* endophthalmitis has also been investigated [146]. In the rabbit model of endophthalmitis, eyes infected with α-toxin- or β-toxin-deficient strains of *S. aureus* were not as inflamed and retained greater retinal function compared to eyes infected with wild-type *S. aureus*, suggesting that these toxins contributed significantly to endophthalmitis virulence [146]. Intravitreal injections of metabolically inactive *S. aureus* and purified *S. aureus* cell wall sacculi led to significant inflammation but did not alter retinal function as measured by electroretinography [43]. Moreover, metabolically inactive *S. aureus* were more inflammogenic than purified sacculi containing only peptidoglycan and lipoteichoic acid, indicating that additional cell wall components were required to cause intraocular inflammation [43].

### *2.2.4 Streptococcus*

Viridans group streptococci and *Streptococcus pneumoniae* are the most common streptococci reported in endophthalmitis [19, 22, 147–149]. Streptococcal endophthalmitis is usually a devastating infection with a poor visual outcome. The incidence of viridans streptococci in endophthalmitis following intravitreal injection has been reported to be three times higher than the incidence in postsurgical endophthalmitis cases, and postinjection cases may be more severe than postoperative cases [150]. Viridans streptococci are also important causes of post-traumatic endophthalmitis [151], especially in children or in rare cases following dental injury [153]; endogenous endophthalmitis, particularly cases secondary to endocarditis [152]; and bleb-related endophthalmitis, where they are the major pathogens in most series. *Streptococcus pneumoniae* endophthalmitis is also an important cause of bleb-related endophthalmitis, accounting for approximately 6 % of cases [154, 155].

Pneumococcal factors which have been shown to contribute to infection virulence include pneumolysin, autolysin, pneumococcal surface protein A, neuraminidase, and capsule [156]. Pneumolysin has been suggested as potential virulence factor in *S. pneumoniae* eye infections. Pneumolysin is a cholesterol-dependent, thiol-activated cytolysin, similar to cytolysins secreted by other gram-positive pathogens such as *Listeria* and *B. anthracis* [157, 158]. Rat eyes injected with purified pneumolysin demonstrated significant dose-dependent anterior and posterior segment inflammation and retinal tissue damage, suggesting that pneumolysin is toxic to the posterior segment of the eye [159]. Further studies showed that infection with pneumolysin-deficient *S. pneumoniae* resulted in significantly less inflammation after 24-h postinfection, but not after 48-h postinfection, when compared to endophthalmitis caused by a wild-type pneumococcus, suggesting that pneumolysin contributed

to the early stages of pneumococcal endophthalmitis [160]. Autolysin is hypothesized to play a direct role in meningitis virulence by mediating the release of inflammatory cell wall components and perhaps the pneumolysin as cells autolyze [161–164]. It is not known whether these events occur in the eye during pneumococcal endophthalmitis. However, endophthalmitis caused by an autolysin-deficient strain of *S. pneumoniae* resulted in less inflammation and clinical pathology at 24- and 48 h postinfection compared to infection caused by wild-type pneumococcus [160]. The specific mechanisms by which pneumolysin and autolysin contribute to endophthalmitis require further investigation.

The capsule of *S. pneumoniae* protects this organism from phagocytosis and killing and is a virulence factor in bacteremia and pneumonia [165–168]. In an experimental rabbit subconjunctival injection model, the pneumococcal capsule did not appear to contribute to the severity of conjunctivitis, and the progression of experimental keratitis was unaffected by the absence of a capsule [169]. In contrast, greater inflammation and higher clinical scores were observed in rabbit eyes intravitreally infected with wild-type pneumococcus when compared to eyes infected with a capsule-deficient strain. Moreover, retinal function was significantly decreased in eyes infected with the wild-type strain compared with eyes infected with the capsule-deficient mutant strain [44]. In contrast to its limited role in anterior segment infection, pneumococcal capsule contributes significantly to virulence during endophthalmitis [44].

### *2.2.5 Gram-Negative Species*

Gram-negative bacteria are highly associated with endogenous endophthalmitis, but are relatively rare in causing endophthalmitis following surgery or trauma. Two extensive reviews by Jackson et al. report that in Asia, endophthalmitis caused by gram-negative bacteria (55 %) was more frequent than endophthalmitis caused by gram-positive bacteria (45 %) [19, 20]. In Europe and North America, the opposite was reported [19, 20]. The most common gram-negative organisms isolated from cases of endogenous endophthalmitis are *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Neisseria meningitis*. Cases of *Salmonella* and *Serratia* endophthalmitis have also been reported, but are rare [19, 20]. Despite improvements in antibiotics and surgical treatment regimens, the visual prognosis associated with these infections remains very poor [19].

*Klebsiella pneumoniae* is a common cause of endogenous endophthalmitis, particularly in East Asian nations. The K1 and K2 serotypes are the two most common serotypes isolated from endogenous *K. pneumoniae* endophthalmitis cases [170]. K1 serotypes contain *magA* and *rmpA* that are associated with the hypermucoviscosity (HMV) phenotype and are important virulence determinants in liver abscesses and other metastatic complications [171, 172]. In experimental endophthalmitis, mouse eyes intravitreally injected with an HMV+ isolate had greater retinal function loss and inflammation compared with that of eyes infected with an HMV− isolate,

suggesting that this phenotype contributed to intraocular virulence [173]. The importance of MagA in endophthalmitis was also confirmed as mouse eyes infected with wild-type *K. pneumoniae* had higher bacterial loads, greater inflammation, and retained significantly less retinal function than eyes infected with an isogenic *magA*-deficient strain [174]. A mouse model of streptozotocin -induced diabetes was also used to demonstrate that retinal vascular permeability in the diabetic ocular environment was associated with *K. pneumoniae* endogenous endophthalmitis. In this study, there was a correlation between the duration of diabetes, the increase in blood-retinal barrier permeability, and the incidence of experimental *K. pneumoniae* endogenous endophthalmitis [175].

*Escherichia coli* and *P. aeruginosa* are other gram-negative bacteria that have been frequently isolated from endogenous endophthalmitis cases. Despite early diagnosis and intervention with intravitreal antibiotics, visual outcomes associated with these infections are almost always poor [19, 20, 176–178]. Not much is known about the virulence factors contributing to the severity of endophthalmitis caused by these gram-negative organisms.

## 2.3 Host-Pathogen Interactions in Endophthalmitis

### *2.3.1 Innate Immune Sensors*

The immune system may be divided into innate and adaptive immune systems. The innate immune system is the more primitive system and is present in both animals and plants, while the adaptive immune system is only present in vertebrates. The innate immune system provides a rapid response system to invading microbes and also signals the adaptive immune system, which then provides a secondary response. The innate immune system does not confer long-lasting immunity, unlike the adaptive immune system. The innate immune system is comprised of cellular and humoral components. Some cells of the innate immune system, such as macrophages and dendritic cells, contain surface or intracellular receptors known as pattern recognition receptors(PRR) that are capable of recognizing "non-self" molecules common to the invading microbial pathogen. These microbial molecules are called pathogen-associated molecular patterns (PAMPs), and different PAMPs are conserved within a class of microbes. An example of the innate immune system's PRR is the Toll-like receptor (TLR) found in macrophages and dendritic cells, and an example of a PAMP is lipopolysaccharide (formerly called "endotoxin"), a component of gram-negative bacteria. Other examples of PAMPs include bacterial flagellin, lipoteichoic acid (found in gram-positive bacteria), and peptidoglycan (a component of bacterial cell walls). The interaction of host cell's PRR with a microbe's PAMP triggers a cascade of immune responses designed to combat the invading microbe.

Experimental animal models have been established to analyze bacterial virulence and the efficacy of various treatments [36–39, 41–46, 69–71, 75, 78, 109–111,

145, 146, 159, 160, 173–175, 179–184]. In acute endophthalmitis, the primary immune cells infiltrating into the posterior segment are neutrophils, which lead to a loss of vitreal clarity. In endophthalmitis and other types of bacterial infections, neutrophil influx is triggered following recognition of the invading pathogen or its byproducts by receptors involved in innate immunity.

Toll-like receptors have been extensively studied, and their contribution in several inflammatory diseases, including ocular infection and inflammation, has been reported [185–197]. The ability of innate immunity to mount an effective inflammatory response depends on the virulence of the infecting organism. The acute inflammatory response either clears an avirulent organism or the organism circumvents inflammation by replicating too rapidly, by forming a biofilm, and/or by producing toxins which may negatively affect inflammatory cell function. The latter scenarios can result in damage to intraocular tissues and loss of vision. The roles of specific components of TLR pathways (individual receptors, adaptors, and proinflammatory mediators) have been studied using transgenic mice deficient in each of these components and have been examined most extensively in *B. cereus* endophthalmitis.

The importance of TLRs has been reported in the context of *S. aureus*, *B. cereus*, and *K. pneumoniae* endophthalmitis [191–197]. Toll-like receptor 2 recognizes bacterial lipoproteins and lipopeptides, while TLR4 recognizes lipopolysaccharides. Toll-like receptor 2 is therefore a major cell surface receptor recognizing gram-positive bacteria, and TLR4 recognizes gram-negative bacteria. Kumar et al. used the mouse model of endophthalmitis to identify a role for TLR2 in inflammation during *S. aureus* infection. The synthetic triacylated lipopeptide Pam3Cys mimics the acetylated amino terminus of bacterial lipopeptides and is a ligand for TLR2. Intravitreal injection of Pam3Cys in this mouse model resulted in upregulated retinal TLR2 expression, as would be expected. The development of severe inflammation in *S. aureus* endophthalmitis was prevented in mouse eyes that were injected with Pam3Cys (which therefore upregulated TLR2) prior to injection of *S. aureus*. Pam3Cys pretreatment also induced the expression of proinflammatory mediators and cathelicidin-related antimicrobial peptide in the mouse retina, potentially via microglial activation [191]. TLR2 is also important in the acute inflammatory response to *B. cereus* endophthalmitis. Novosad et al. reported that TLR2−/− mice infected with *B. cereus* had lower concentrations of proinflammatory mediators and reduced recruitment of neutrophils in the posterior segment, resulting in less intraocular inflammation and retinal tissue destruction compared with endophthalmitis in wild-type mice [195]. Taken together, these studies suggested the importance of TLR2 in the innate response to these two important gram-positive endophthalmitis pathogens.

Toll-like receptor 5 is the only protein-binding TLR that is conserved in vertebrates [198–200]. Flagellin, the protein that constitutes bacterial flagella, is the major ligand of TLR5 [200]. TLR5 has been investigated as an anti-inflammatory target in several disease models, including cystic fibrosis [201], rheumatoid arthritis [202], and colitis [203]. In terms of ocular infections, flagellin-mediated protection has been used as a prophylactic approach for preventing *P. aeruginosa* keratitis

[193, 204]. As stated above, *B. cereus* migrates within the eye during infection, with flagella as its primary means of locomotion. Unexpectedly, *B. cereus* flagellin was a weak agonist for TLR5, both in vitro and in vivo, compared to control *Salmonella* flagellin, a potent agonist for TLR5. TLR5 was also found to have a limited role in inciting inflammation during *B. cereus* endophthalmitis despite the presence of flagella on its surface [196]. The role of TLR5 in the pathogenesis of endophthalmitis caused by flagellated gram-negative pathogens such as *E. coli* or *P. aeruginosa* has not been explored.

Toll-like receptors together with interleukin-1 (IL-1) receptors form a receptor superfamily called Toll/IL-1. Toll-like receptor intracellular signaling is regulated by a complex signaling pathway that is mediated by adaptor molecules that ultimately trigger an immunostimulatory response based upon interactions with a specific ligand. The majority of TLRs are dependent upon a common signaling pathway mediated by the adaptor molecule myeloid differentiation gene 88 (MyD88), while other TLRs depend on a different adaptor, TRIF (Toll/IL-1 receptor domain-containing adaptor-inducing interferon β). Experimental *B. cereus* endophthalmitis in MyD88–/– mice demonstrated significantly less inflammation and less retinal damage compared to that of wild-type infected controls [205]. A similar result was also reported in MyD88–/– mice infected with *S. aureus* [194]. Surprisingly, mice deficient in TRIF or in its receptor, TLR4, also had significantly less intraocular inflammation during experimental *B. cereus* endophthalmitis. These studies identified the importance of the TLR4/TRIF pathway in *B. cereus* infection [205]. This finding was unexpected and novel, as the canonical ligand for TLR4/TRIF is lipopolysaccharide, which is not found in *B. cereus* or other gram-positive pathogens.

Toll-like receptor 4 has been implicated in the pathogenesis of gram-negative endophthalmitis because these bacteria have lipopolysaccharide. *K. pneumoniae* has lipopolysaccharide in its outer cell wall which may be sensed by TLR4. In *K. pneumoniae*-infected TLR4–/– mice, the delay in recruitment of neutrophils to the eye was attributed to lower concentrations of proinflammatory mediators in infected eyes compared to that in eyes of wild-type control mice. Proinflammatory mediators KC, MIP-1α, and TNF-α (tumor necrosis factor alpha) were significantly decreased in infected TLR4–/– eyes when compared to infected controls. These results suggest the importance of TLR4 in the early recruitment of infiltrating neutrophils during experimental *K. pneumoniae* endophthalmitis [197].

In addition to TLRs, other innate receptors such as NOD-like receptors (NLRs) and RIG-1-like receptors (RLRs) recognize pathogens and initiate an inflammatory response during bacterial infection [207]. NOD-like receptors, including NOD1 and NOD2, are expressed in the eye [208, 209]. Moreover, there are other endogenous, nonmicrobial *d*amage-*a*ssociated *m*olecular *p*atterns (DAMPs) released from damaged tissue or dying cells that are able to initiate an immune response [210]. DAMPs, including hyaluronic acid, HSPs, HMGB-1, and S100 proteins, are located in the ocular tissues and are shown to be involved in intraocular inflammation [211–214]. The roles of these additional innate sensors in acute inflammation during endophthalmitis have yet to be studied.

### 2.3.2 Immune Mediators and Responders

Pro-inflammatory mediators are synthesized by neutrophils and other cells in response to infection and thus initiate the inflammatory response. Early studies in a *S. aureus* endophthalmitis rat model [215] reported that TNF-α, IL-1β (interleukin 1β), cytokine-induced neutrophil chemoattractant CINC (rat chemokine equivalent to human IL8), and IFN-γ (interferon gamma) expression peaked in the vitreous at 24 h after *S. aureus* infection. This response correlated with peaks of clinical inflammatory signs, such as anterior chamber inflammatory cells and fibrin, posterior synechia, and vitreous exudate [215–217]. Cytokine concentrations also peaked at 24-h postinfection following infection of rat eyes with *S. epidermidis*. This peak also correlated with increased clinical inflammatory signs, such as fibrin in the anterior chamber, iris synechiae, hypopyon, and loss of red reflex [218]. In the experimental *B. cereus* mouse model of endophthalmitis, cytokines TNF-α, IL-1β, IL6, and MIP1 and chemokine KC (CXCL1) increased significantly in parallel with neutrophil infiltration and blood-retinal barrier permeability [184, 195, 219]. Thus, the time course of increasing cytokine and chemokine levels is closely associated with a deteriorating clinical presentation in endophthalmitis models, suggesting the importance of proinflammatory mediators in driving inflammation and the overall course of endophthalmitis.

Ramadan et al. [206] reported on the importance of TNF-α in the acute response to experimental *B. cereus* endophthalmitis. In the eyes of TNF-α–/– mice, *B. cereus* replicated more quickly, retinal function declined more rapidly, and fewer PMNs were recruited to the site of infection compared to that of infected wild-type mice. Unpublished studies from our research group also suggest that in the absence of the chemokine KC/CXCL1, neutrophil influx and disease pathogenesis are reduced in experimental *B. cereus* endophthalmitis. In contrast, in the absence of IL6, inflammation in experimental *B. cereus* endophthalmitis is not reduced, suggesting different roles for KC/CXCL1 and IL6 in this disease.

Figure 2.1 depicts the contribution of specific components of TLR pathways (TLRs, adaptors TRIF and MyD88, and proinflammatory mediators TNF-α, IL6, and KC/CXCL1) to infection during experimental *B. cereus* endophthalmitis. In these experiments, mouse eyes were intravitreally injected with 100 colony-forming units (CFU) of *B. cereus*. At 12-h postinfection, eyes were harvested for histology as described previously [173, 174, 184, 195–197, 206, 219]. Mouse strains included C57BL/6 J mice (Jackson Laboratories) and the following mutant strains derived on the C57BL/6 J background: TLR2–/– [195], TLR4–/– [205], TLR5–/– [196], TRIF–/– [205], MyD88 [205], TNFα–/– [206], KC/CXCL1–/– (a kind gift from Dr. Sergio Lira), and IL6–/– (Jackson Laboratories). At 12-h postinfection, C57BL/6 J eyes exhibited severe posterior segment inflammation, retinal destruction, maximal bacterial growth, and loss of retinal function below 20 %. Endophthalmitis in eyes of TLR5–/–, TNF-α–/–, and IL6–/– mice achieved similar levels of severity. In contrast, inflammation and retinal damage in infected eyes of TLR2–/–, TLR4–/–, TRIF–/–, MyD88–/–, and KC/CXCL1–/– mice was signifi-

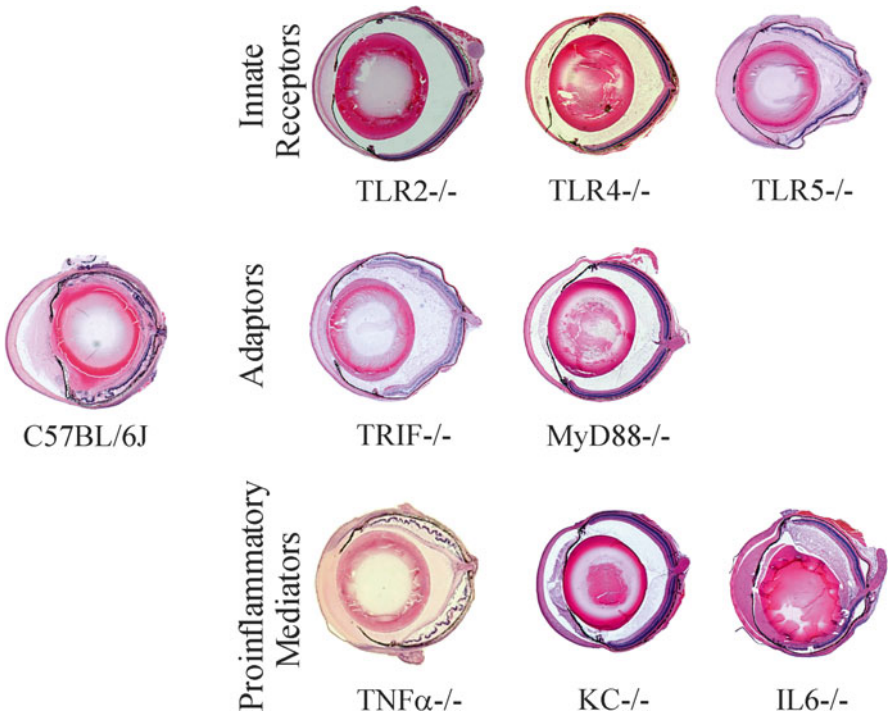


**Fig. 2.1** Innate immunity and *Bacillus cereus* endophthalmitis. This figure illustrates the contribution of specific components of Toll-like receptor (*TLR*) pathways to infection during experimental *B. cereus* endophthalmitis in mice. As detailed in the text, mouse strain C57BL/6 J and variant strains based on this platform that were deficient in either certain TLRs (TLR2, TLR4, TLR5), adaptors (TRIF, MyD88), or proinflammatory cytokines (TNF-α, KC) or chemokines (IL6) were used. Eyes in each strain of mice were intravitreally injected with *Bacillus cereus* bacteria and harvested for histology 12 h later. Eyes from C57BL/6 J mice and from strains deficient in TLR5, TNF-α, or IL6 showed a similar amount of severe inflammation, bacterial growth, and retinal destruction. In contrast, eyes from the remaining strains showed far less inflammation and retinal destruction. This illustrates the important role of TLR2, TLR4, their adaptors TRIF and MyD88, and proinflammatory mediators TNF-α and KC/CXCL1 in the pathogenesis of *B. cereus* endophthalmitis. Sections are representative of at least three eyes per time point and at least two independent experiments. Magnification, 10×. Permissions: TLR2−/− section (PLoSOne, 198), TLR5−/− section (PLoSOne, 199), TNFα−/− section (© Investigative Ophthalmology and Visual Sciences, 209)

cantly reduced at 12-h postinfection. This comparison demonstrates the importance of TLR2, TLR4, their adaptors TRIF and MyD88, and proinflammatory mediators TNF-α and KC/CXCL1 in the pathogenesis of *B. cereus* endophthalmitis.

Neutrophils are the predominant infiltrating immune cells in the posterior segment and retina during endophthalmitis. This is the case for endophthalmitis caused by a number of species, such as *S. aureus* [216, 217], *B. cereus* [184, 195, 196], *K. pneumoniae* [197], *E. faecalis* [71, 78], and *S. pneumoniae* [44]. In a *S. aureus* rat endophthalmitis model, neutrophil depletion by antineutrophil antibody early in the

course of infection led to significantly lower clinical scores and less vitreal inflammation, suggesting that barring neutrophils from the eye may be an effective way to prevent damaging sequelae from inflammation [217], as long as sterilizing antibiotics are also employed.

There is only limited information on the extent and importance of antibody responses during endophthalmitis. In an experimental *S. aureus* endophthalmitis rat model where 65 viable organisms were intravitreally injected, immunoglobulin titers produced in response to ribitol teichoic acid, the major antigenic determinant of *S. aureus* cell wall, were detected. Immunoglobulin M (IgM) titers to ribitol teichoic acid increased in serum and vitreous, with a maximal IgM response on day 21 postinfection. A weak IgG response in serum and vitreous was also reported [216]. In a *S. aureus* rabbit endophthalmitis model, a strong IgG response was detected in serum, aqueous, and vitreous in response to ribitol teichoic acid. In addition, there was an IgA antibody response in tears and vitreous but not in serum [220]. A low antibody response to intravitreal injection of *S. epidermidis* in rabbits has also been reported [221].

### *2.3.3 Complement and Apoptosis*

The complement cascade includes a network of serum and membrane-associated proteins that work in concert to elicit inflammatory and cytolytic responses to infectious organisms. Upon microbial recognition, this cascade generates potent proinflammatory mediators (anaphylatoxins), mediates opsonization of the pathogen through various opsonins, attracts phagocytic inflammatory cells to site of infection, and lyses pathogens through the assembly of the membrane attack complex [222–224]. Bacterial cell wall components, such as lipopolysaccharide, can activate complement [224]. In an uninfected host, complement components are constantly deposited on self-tissue in small quantities, but are present in greater quantities during inflammation [225]. In the healthy human eye, tight regulation of the complement system by complement regulatory proteins limits damage to self-tissue during activation [226–231]. Clinical reports indicate that patients had elevated levels of activated complement in the aqueous humor [232, 233] during severe uveitis and in the vitreous during vitreal inflammation [234].

The role of complement in endophthalmitis has been investigated in different animal models. Early studies investigated endophthalmitis in guinea pigs made complement deficient with cobra venom factor [183]. Partially complement-deficient guinea pigs had an impaired intraocular host defense to *P. aeruginosa*, a condition which was restored when complement levels returned to normal. Eyes of complement-deficient guinea pigs infected with *S. epidermidis* or *S. aureus* had higher bacterial loads and severe inflammation compared to that of infection in control guinea pigs, and again this effect was restored when complement levels returned to normal [235]. More recent studies were conducted to understand the role of C3, a central component essential for activation of effectors of complement

activation. In infected C3−/− mice, the overall course of infection and inflammation was not different from that of infected wild-type mice, suggesting that the complement pathway may not contribute significantly to the course of endophthalmitis [236]. The differences between experimental outcomes in C3−/− and cobra venom factor-treated mice were attributed to the fact that cobra venom factor-mediated depletion of complement had global negative effects on the physiology of the experimental animals, including their immune systems. These studies also highlighted the importance of directly testing the contribution of single immune factors in infection models where the multifactorial nature of inflammation can be confounding.

Apoptosis is a form of controlled cell death in which segmentation of a cell into apoptotic bodies leads to their phagocytosis [237]. In the healthy eye, Fas ligand is constitutively expressed and contributes to the maintenance of immune privilege by inducing apoptosis of infiltrating T lymphocytes during an adaptive response [238]. In a mouse model of experimental *S. aureus* endophthalmitis, wild-type mice were able to clear an infection initiated by 500 *S. aureus*, while Fas ligand-deficient mice were unable to clear an infection initiated with the same inoculum [236]. In the absence of FasL, fewer neutrophils infiltrated into the eye and *S. aureus* grew more rapidly [236], suggesting that Fas ligand is critical in neutrophil recruitment and staphylococcal clearance. In an experimental model of *S. epidermidis* endophthalmitis, retinal apoptosis correlated significantly with upregulation of proapoptotic proteins Bax and Fas in ganglion cells, bipolar cells, and photoreceptor cells [239]. Apoptotic bodies were detected in these retinal cell types in *S. epidermidis*-infected eyes. Intraocular inflammation peaked at 24-h postinfection, apoptotic Bax and Fas expression peaked at 48 h, and apoptosis in the retina peaked at 72-h post-infection. These data provide evidence that retinal Bax and Fas expression is involved in apoptosis in *S. epidermidis* experimental endophthalmitis [239]. These studies agree with the finding that bound Fas ligand activates innate immunity, while soluble Fas ligand is immunosuppressive [240]. An equilibrium between the various forms of Fas ligand exists and is likely vital in modulating inflammation initiated by bacteria. However, apoptotic retinal cell death may not occur in endophthalmitis caused by all bacterial species. *Bacillus cereus* infection of retinal pigment epithelial cell monolayers resulted primarily in necrotic cell death [42], but it is not known whether this extends to in vivo infection. Necrotic cell death may be a hallmark of rapid and severe forms of endophthalmitis, such as those caused by *B. cereus*.

## 2.4 Comparative Analysis of Experimental Endophthalmitis

As previously mentioned, the virulence of the causative bacterium plays a vital role in determining the outcome of infection. Infection caused by an avirulent organism usually leads to mild inflammation and no significant loss of vision. A healthy ocular immune response may spontaneously clear the infection or antibiotics quickly sterilize the eye, and vision is minimally impaired. However, infection caused by a virulent organism can lead to significant inflammation, loss of vision, and an

infection that may be refractory to treatment. Differences in virulence may be attributed to the plethora of toxins and other factors secreted by the bacterium or its growth rate or behavior in the eye. Even among pathogens, differences in virulence and infection outcome exist. The host response triggered in the eye in response to unimpeded bacterial growth or components of the cell wall may also damage tissue. The multifactorial nature of this disease makes successful treatment difficult, especially in severe cases.

Research conducted to understand bacterial ocular virulence strategies and interactions between the host and pathogen highlight similarities in the pathogenesis of endophthalmitis caused by different virulent bacteria. A comparative analysis of these experimental models is illustrated in Fig. 2.2. In general, invading bacteria are recognized by innate immune receptors and an inflammatory response ensues. Pathogens replicate in the vitreous, even as inflammatory cells enter the eye in an attempt to control the infection. Proinflammatory mediators recruit more inflammatory cells into the posterior segment. Pathogens synthesize one or more toxins which are essential for virulence. Eventually, retinal function declines, which may be attributed to toxins or byproducts of the inflammatory response negatively affecting the retina, and/or to the mass of bacteria and inflammatory cells blocking the light path to the retina.

Figure 2.2 illustrates a comparative analysis of infection progress and parameters in experimental animal models of *B. cereus*, *K. pneumoniae*, *S. epidermidis*, *S. pneumoniae*, *E. faecalis*, and *S. aureus* endophthalmitis, based on references cited in this chapter. In the first panel, a general indicator of disease progression of experimental endophthalmitis is depicted. In general, *B. cereus* endophthalmitis progresses more rapidly toward severity than does *K. pneumoniae*, *S. pneumoniae*, *E. faecalis*, and *S. aureus*. In contrast, *S. epidermidis* endophthalmitis progresses to its maximum severity with time, then resolves spontaneously in rabbit eyes (in contrast with untreated infection in human eyes). In the second panel, intraocular bacterial growth represented. *Bacillus cereus* grew from 100 to $10^8$ CFU/eye by 12-h postinfection [43, 184, 195, 196]. *Klebsiella pneumoniae* grew from 100 to $10^8$ CFU/eye by 24-h postinfection [173, 174, 197]. In the *S. epidermidis* model, an inoculum of 3800 CFU reached a peak of $10^5$–$10^7$ CFU/ml at 8–12-h postinfection, with declines in CFU by 48-h postinfection [109]. In the *S. pneumoniae* model, an inoculum of 340–540 CFU reached a peak of $10^8$ CFU/ml at 24 h, with gradual declines to $10^6$ CFU/ml at 48-h postinfection [44]. *Enterococcus faecalis* grew from 100 to $10^8$ CFU/eye by 24-h postinfection [43], while *S. aureus* grew to the same concentration by 48-h postinfection [43]. The third panel depicts intraocular inflammation during experimental endophthalmitis, which combines inflammatory cell influx with detection of proinflammatory mediators in the eye. In *B. cereus* endophthalmitis, neutrophils and proinflammatory mediators increase in the eye between 4- and 12-h postinfection [184, 195, 196]. *Klebsiella pneumoniae* has a more gradual increase in these inflammation parameters over time, from 3- to 24-h postinfection [174, 197]. With a higher inoculum of 7000 *S. epidermidis*, neutrophils and mediator levels peaked at 24 h with a gradual decrease thereafter [218]. Neutrophils and inflammatory mediators peaked at 36-h postinfection in *S. aureus* endophthalmitis

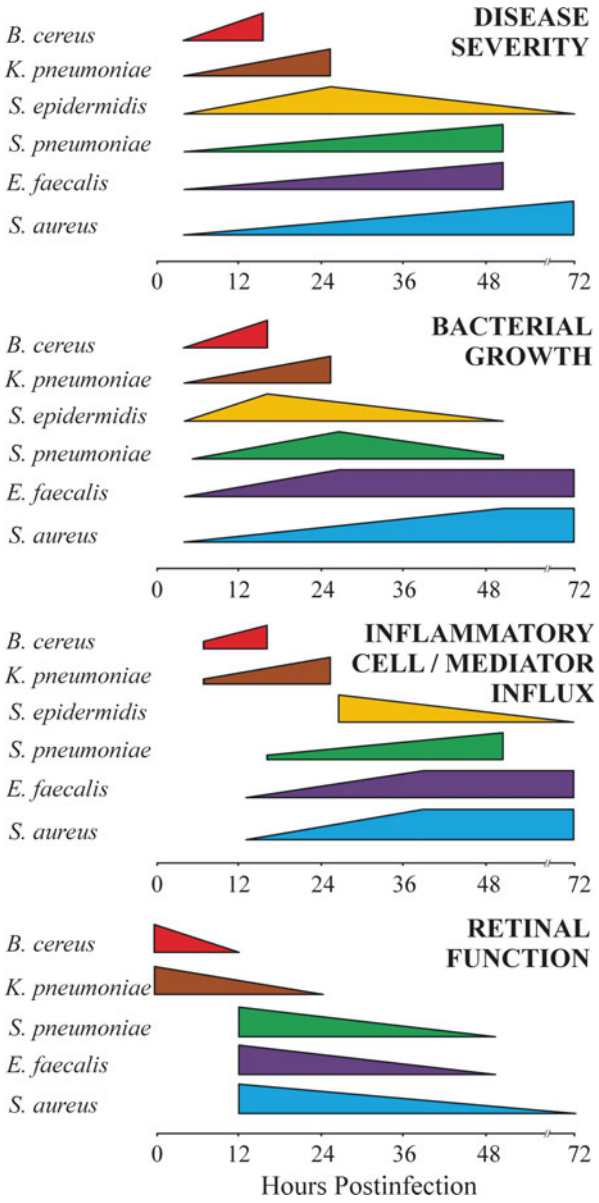


**Fig. 2.2** Comparative analysis of experimental bacterial endophthalmitis. This figure illustrates a comparative analysis of infection progress and parameters in experimental animal models of *B. cereus*, *K. pneumoniae*, *S. epidermidis*, *S. pneumoniae*, *E. faecalis*, and *S. aureus* endophthalmitis, based on references cited in this chapter. The time frame represents the course of infection, beginning with an intravitreal injection of organisms (time 0) and the latest time analyzed in published models (72 h), which generally indicates complete loss of vision and severe inflammation. The maximum values are a theoretical maximum for each parameter specific to each species, but not compared among species (see text)

[215], while neutrophils peaked at this same time in *E. faecalis* endophthalmitis [43]. The fourth panel represents retinal function loss as measured by electroretinography. For *B. cereus* endophthalmitis, retinal function was almost completely lost by 12-h postinfection [43, 184, 195, 196]. Comparatively, other organisms caused retinal function loss more slowly. Retinal function was lost over a 24-h duration with *K. pneumoniae* [174, 197], over a 48-h duration with *S. pneumoniae* [44] and *E. faecalis* [43, 71], and over a 72-h duration with *S. aureus* [43].

Comparing experimental models also highlights important differences in endophthalmitis pathogenesis which are critical for successful treatment. For example, *B. cereus* endophthalmitis almost always causes significant intraocular inflammation and vision loss which, as experimental studies have shown [241, 242], requires immediate and aggressive treatment for a successful visual outcome. Compared with other endophthalmitis pathogens, *B. cereus* replicates more rapidly and causes a more explosive inflammatory response, and vision loss occurs within hours instead of days (Fig. 2.2). For other endophthalmitis pathogens, the window of opportunity for adequate treatment is much longer than for *B. cereus*. It is therefore reasonable to posit that aggressive therapeutic strategies which are successful for *B. cereus* would also be beneficial for endophthalmitis that evolves more slowly. Such a therapeutic strategy would include antibiotics which kill rapidly but are not toxic to the eye, drugs which suppress the negative effects of inflammation, and drugs which neutralize damaging toxins secreted by these organisms.

## 2.5 Conclusions

Although endophthalmitis is a relatively rare infection, the potential for vision loss is significant. For the most part, the important virulence determinants of endophthalmitis pathogens have been identified, but the mechanisms by which these factors damage tissue and cause inflammation are still being investigated. A clearer picture of the interactions between innate immunity and a few endophthalmitis pathogens has emerged. However, a detailed understanding of intraocular inflammation pathways common to these pathogens is critical for designing anti-inflammatory strategies which are more effective. Also of need is the experimental testing and clinical use of antibiotics which sterilize the eye at a rate superior to those currently in use. The motivation for continued research in this area is the fact that, despite current therapies, endophthalmitis continues to cause vision loss. The development of better therapeutic strategies for endophthalmitis will be based directly on knowledge gained from the aforementioned experimental studies, with the focus on bacterial clearance, reducing inflammation, and preventing tissue damage regardless of the virulence of the infecting pathogen.

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# Chapter 3
# Microbiologic Diagnosis in Endophthalmitis

**Darlene Miller**

## 3.1 Introduction

Endophthalmitis is an infection involving the vitreous body and/or aqueous humor [1–3]. Greater than 70 % of endophthalmitis cases are healthcare related. Infections occur following intraocular surgery (cataract surgery, glaucoma drainage device implantation, filtering bleb surgery, keratoplasty, keratoprosthesis), open globe trauma, and intravitreal injections for the management of a number of retinal diseases [1–20].

Healthcare-associated endophthalmitis may be classified according to clinical course (acute vs chronic), route (exogenous vs endogenous), or type of surgery/source (bleb-associated, intravitreal injections). Community-associated exogenous endophthalmitis usually follows eye trauma but may occur after bacteremia or fungemia from a community-acquired infection (e.g., endocarditis, pyelonephritis) or intravenous drug use. Presenting clinical signs of infectious endophthalmitis vary by type of ocular healthcare or community-associated exposure, prior surgical intervention, the infecting microorganism, the associated inflammation, and the duration of the disease [1, 6, 7, 11, 13, 15, 18, 21–23].

Both healthcare-associated and community-acquired endophthalmitis cases are rare events. The intraocular chambers are well protected by the orbit and surrounding tissues and structures. A breach of the cornea or sclera via surgery or trauma, or of the blood-eye barrier via metastatic spread, must occur for microorganisms to enter the aqueous or vitreous and multiply. The aqueous and vitreous fluids are excellent

D. Miller, DHSC, MPH, CIC
Department of Ophthalmology and Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami, FL 33136, USA

Bascom Palmer Eye Institute, Miami, FL, USA
e-mail: dmiller@miami.edu



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culture media. Any organism gaining entrance to the intraocular chambers can then multiply and initiate disease [24].

The number of endophthalmitis cases and spectrum of causative agents are expanding. The frequency and diversity of microbial agents recovered in endophthalmitis is influenced by the type of endophthalmitis, quality and quantity of collected specimen, and diagnostic method used for recovery and confirmation [1–3, 10, 25, 26].

## 3.2 Epidemiology

More than 140 (Table 3.1) organisms have been recovered from intraocular fluids of patients with clinical endophthalmitis. The greatest diversity is found among isolates from postcataract and endogenous cases. Bacterial pathogens are the predominant etiological agents recovered from all types of endophthalmitis. Among the bacteria, gram-positive organisms such as staphylococci and streptococci predominate, both by traditional culture and newer culture-dependent and culture-independent techniques [26].

### *3.2.1 Staphylococci*

Staphylococci make up more than 70 % of bacteria recovered from cases of healthcare- and community-associated endophthalmitis. A recent classification schema for the genus *Staphylococcus* listed 47 different species and 23 subspecies that are associated with animals or humans; most are coagulase-negative staphylococci [27]. Only one human-associated species, *Staphylococcus aureus*, is coagulase-positive. Reservoirs for staphylococci include the skin and mucus membranes of humans. Staphylococci also colonize the skin and mucous membranes of cats and dogs which can be transmitted to humans [27–31].

### *3.2.2 Streptococci*

Streptococci are a heterogeneous group composed of alpha hemolytic, beta hemolytic, and nonhemolytic species. Alpha hemolysis refers to the "greening" of agar beneath bacterial colonies grown on blood agar plates, while beta hemolytic colonies cause complete hemolysis with resulting clear zones in the agar beneath colonies. Viridans streptococci (from Latin "viridis," green) are sometimes called "alpha hemolytic streptococci" or "alpha streptococci" because most species exhibit alpha hemolysis. Viridans streptococci are not a specific genus and species but rather are a group of bacteria. Viridans streptococci are the most frequent members

**Table 3.1** Spectrum and diversity of microbial pathogens recovered from infectious endophthalmitis

| Pathogens recovered from endophthalmitis | Clinical endophthalmitis types | | | | | | | | | | | Key |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Groups | Acute-onset postoperative (rate—.03–.2 %) | Bleb associated (rate—0.17–13.2 %) | Delayed-onset postoperative (rate—0.02 %) | Keratitis associated (rate—0.2 .4 %) | Post-intravitreal (rate—0.02–.09 %) | KPro-related rate (0–12 %) | Endogenous | Glaucoma drainage device (rate—0.11–0.5 %) | Trauma (rate—2–12 %) | | |
| *Abiotrophia defectiva* | 1 | 1 | 1 | | | 1 | | 1 | | | 1 | Gram-positive bacteria |
| *Agrobacterium radiobacter* | 1 | 1 | | | | | | | | | | |
| *Bacillus cereus* | 1 | | 1 | | 1 | | | 1 | 1 | 1 | 2 | Gram-negative bacteria |
| *Bacillus circulans* | 1 | | 1 | | 1 | | | 1 | | 1 | | |
| *Bacillus mycoides* | 1 | | 1 | | 1 | | | 1 | | 1 | 3 | Mycobacteria |
| *Bacillus* species | 1 | | 1 | | 1 | | | 1 | | 1 | | |
| *Clostridium perfringens* | 1 | | | | | | | | | 1 | 4 | Actinomycetes |
| *Clostridium sordellii* | 1 | | | | 1 | | | | | | | |
| *Clostridium subterminale* | 1 | | | | | | | 1 | | | 5 | Yeasts |
| Coagulase-negative staphylococci[a], not speciated | 1 | 1 | 1 | 1 | | | 1 | | | 1 | | |
| *Corynebacterium aquaticum* | 1 | 1 | | 1 | | | | | | 1 | 6 | Filamentous fungi (molds) |
| *Corynebacterium macginleyi* | 1 | 1 | | 1 | | | | | | 1 | | |

(continued)

**Table 3.1** (continued)

| Pathogens recovered from endophthalmitis | Clinical endophthalmitis types | | | | | | | | | | | Key |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Groups | Acute-onset postoperative (rate—.03–.2 %) | Bleb associated (rate—0.17–13.2 %) | Delayed-onset postoperative (rate—0.02 %) | Keratitis associated (rate—0.2 .4 %) | Post-intravitreal (rate—0.02–.09 %) | KPro-related rate (0–12 %) | Endogenous | Glaucoma drainage device (rate—0.11–0.5 %) | Trauma (rate—2–12 %) | | |
| *Corynebacterium minutissimum* | 1 | 1 | | | | | | | | | 7 | Protozoa |
| *Corynebacterium* species | 1 | 1 | | 1 | | | | | | 1 | | |
| *Corynebacterium striatum* | 1 | 1 | | 1 | | | | | | 1 | | |
| *Corynebacterium xerosis* | 1 | 1 | | | | | | | | 1 | | |
| *Enterococcus casseliflavus* | 1 | | | | | | | 1 | | 1 | | |
| *Enterococcus faecalis* | 1 | 1 | 1 | | 1 | | | 1 | | | | |
| *Gemella haemolysans* | 1 | 1 | | | 1 | | | | | | | |
| *Gemella morbillorum* | 1 | | | | | | | | 1 | | | |
| *Granulicatella adiacens* | 1 | 1 | | | | 1 | | | | | | |
| *Listeria monocytogenes* | 1 | | | | | | | 1 | | | | |
| *Micrococcus* species | 1 | 1 | | | | | | 1 | | | | |
| *Peptostreptococcus* | 1 | | | | | | | 1 | | | | |
| *Peptostreptococcus prevotii* | 1 | | | | | | | 1 | | | | |
| *Propionibacterium acnes* | 1 | | | 1 | 1 | 1 | | 1 | | | | |
| *Propionibacterium avium* | 1 | | | 1 | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Propionibacterium granulosum* | 1 | | | 1 | | | | | | | | |
| *Staphylococcus chromogenes*[a] | 1 | | | | | 1 | | | | | | |
| *Staphylococcus saprophyticus* | 1 | | | | | 1 | | | | | | |
| *Staphylococcus aureus* | 1 | 1 | 1 | | 1 | 1 | 1 | 1 | | | | |
| *Staphylococcus capitis* | 1 | 1 | | | | 1 | | | | | | |
| *Staphylococcus cohnii* | 1 | 1 | | | | 1 | | 1 | | | | |
| *Staphylococcus epidermidis* | 1 | 1 | 1 | | | 1 | | | | 1 | | |
| *Staphylococcus lugdunensis* | 1 | 1 | | | | 1 | | | | | | |
| *Staphylococcus sciuri* | 1 | 1 | | | | 1 | | | | | | |
| *Staphylococcus simulans* | 1 | 1 | | | | 1 | | | | | | |
| *Staphylococcus warneri* | 1 | 1 | | | | 1 | | | | | | |
| *Staphylococcus xylosus* | 1 | 1 | | | | 1 | | | | | | |
| *Staphylococcus auricularis* | 1 | 1 | | | | 1 | | | | | | |
| *Staphylococcus hominis* | 1 | 1 | | | | 1 | | | | | | |
| *Streptococcus bovis* | 1 | | | | | 1 | | | | | | |
| *Streptococcus acidominimus* | 1 | | | | | 1 | | | | | | |
| *Streptococcus agalactiae* (group B) | 1 | 1 | 1 | | | 1 | | 1 | | | | |

(continued)

**Table 3.1** (continued)

| Pathogens recovered from endophthalmitis | Clinical endophthalmitis types | | | | | | | | | | | Key |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Groups | Acute-onset postoperative (rate—.03–.2 %) | Bleb associated (rate—0.17–13.2 %) | Delayed-onset postoperative (rate—0.02 %) | Keratitis associated (rate—0.2 .4 %) | Post-intravitreal (rate—0.02–.09 %) | KPro-related rate (0–12 %) | Endogenous | Glaucoma drainage device (rate—0.11–0.5 %) | Trauma (rate—2–12 %) | | |
| *Streptococcus anginosus* | 1 | | | | | 1 | | | | | | |
| *Streptococcus bovis* | 1 | | | | | 1 | | | | | | |
| *Streptococcus constellatus* | 1 | | | | | 1 | | | | | | |
| *Streptococcus dysgalactiae* | 1 | | | | | 1 | | | | | | |
| *Streptococcus equisimilis* | 1 | | | | | 1 | | 1 | | | | |
| *Streptococcus intermedius* | 1 | | | | | 1 | | | | | | |
| *Streptococcus mitis* | 1 | 1 | 1 | | | 1 | | | | | | |
| *Streptococcus mutans* | 1 | | | | | 1 | | | | | | |
| *Streptococcus oralis* | 1 | 1 | 1 | | | 1 | | | | | | |
| *Streptococcus pneumoniae* | 1 | 1 | 1 | | 1 | 1 | 1 | 1 | 1 | | | |
| *Streptococcus pyogenes* (group A) | 1 | | | | | | | 1 | | | | |
| *Streptococcus salivarius* | 1 | | | | | 1 | | | | | | |
| *Streptococcus sanguinis* | 1 | 1 | 1 | | | 1 | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Streptococcus sanguis* | 1 | 1 | 1 | | | 1 | | | | | | |
| Viridans streptococcus group[b], not speciated | 1 | 1 | 1 | | | 1 | | | 1 | | | |
| *Achromobacter xylosoxidans* | 2 | | | | 1 | | | | | | | |
| *Acinetobacter* species | 2 | 1 | | | | | | | | | | |
| *Aggregatibacter actinomycetemcomitans* | 2 | | | | | | | 1 | | | | |
| *Bacteroides distasonis* | 2 | | | | | | | 1 | | | | |
| *Bacteroides* species | 2 | 1 | | | | | | 1 | | | | |
| *Burkholderia cepacia* | 2 | 1 | | | 1 | | | 1 | | | | |
| *Capnocytophaga* species | 2 | 1 | | | | | | 1 | | | | |
| *Citrobacter freundii* | 2 | 1 | | | | | | 1 | | 1 | | |
| *Citrobacter koseri* | 2 | 1 | | | | | | 1 | | 1 | | |
| *Enterobacter aerogenes* | 2 | 1 | | | | | | | | 1 | | |
| *Enterobacter cloacae* complex | 2 | 1 | | | | | | 1 | | 1 | | |
| *Escherichia coli* | 2 | 1 | | | | 1 | 1 | 1 | | 1 | | |
| *Flavobacterium* species | 2 | | | | 1 | | | | | | | |
| *Haemophilus influenzae* | 2 | 1 | 1 | 1 | | 1 | | 1 | 1 | | | |
| *Klebsiella oxytoca* | 2 | | | | | | | 1 | | | | |
| *Klebsiella pneumoniae* | 2 | | | | | | | 1 | | 1 | | |
| *Moraxella catarrhalis* | 2 | | 1 | | | | | | 1 | | | |
| *Moraxella lacuna* | 2 | | 1 | | | | | | 1 | | | |
| *Moraxella osloensis* | 2 | | 1 | | | | | | 1 | | | |

(continued)

**Table 3.1** (continued)

| Pathogens recovered from endophthalmitis | Clinical endophthalmitis types | | | | | | | | | | | Key |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Groups | Acute-onset postoperative (rate—.03–.2 %) | Bleb associated (rate—0.17–13.2 %) | Delayed-onset postoperative (rate—0.02 %) | Keratitis associated (rate—0.2 .4 %) | Post-intravitreal (rate—0.02–.09 %) | KPro-related rate (0–12 %) | Endogenous | Glaucoma drainage device (rate—0.11–0.5 %) | Trauma (rate—2–12 %) | | |
| *Moraxella* species | 2 | | 1 | | | | | | 1 | | | |
| *Morganella morganii* | 2 | 1 | | | | | | | | | | |
| *Neisseria meningitidis* | 2 | | | | | | | 1 | | | | |
| *Neisseria mucosa* | 2 | | | | | | | 1 | | | | |
| *Ochrobactrum anthropi* | 2 | 1 | | 1 | | | | 1 | | | | |
| *Pantoea agglomerans* | 2 | 1 | | | | 1 | | 1 | | | | |
| *Proteus mirabilis* | 2 | 1 | | | 1 | 1 | 1 | | | | | |
| *Proteus vulgaris* | 2 | 1 | | | | | | | | | | |
| *Pseudomonas aeruginosa* | 2 | 1 | 1 | 1 | 1 | | 1 | 1 | 1 | 1 | | |
| *Pseudomonas stutzeri* | 2 | | | 1 | | | | | | | | |
| *Rhizobium radiobacter* | 2 | | | | 1 | 1 | | | | | | |
| *Salmonella* group B | 2 | | | | | 1 | | 1 | | | | |
| *Salmonella typhi* | 2 | | | | | 1 | | | | | | |
| *Serratia marcescens* | 2 | 1 | 1 | | 1 | | 1 | 1 | 1 | | | |
| *Sphingomonas paucimobilis* | 2 | | | | | | | | | | | |
| *Stenotrophomonas maltophilia* | 2 | 1 | | | | | | | | 1 | | |
| *Weeksella virosa* | 2 | 1 | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Mycobacterium abscessus* | 3 | | | | 1 | | | | | | | |
| *Mycobacterium chelonae* group | 3 | | | | | 1 | | | | | | |
| *Mycobacterium fortuitum* | 3 | 1 | | | 1 | | | | | | | |
| *Mycobacterium mucogenicum* | 3 | | | | 1 | | | | | | | |
| *Mycobacterium triplex* | 3 | | | 1 | | | | | | | | |
| *Actinomyces neuii* | 4 | 1 | | | | | | | | | | |
| *Nocardia asteroides* complex | 4 | 1 | | | 1 | | | | | 1 | | |
| *Nocardia brasiliensis* complex | 4 | | | | | | | | | 1 | | |
| *Nocardia farcinica* | 4 | | | | | | | 1 | | 1 | | |
| *Streptomyces* species | 4 | | | | | 1 | | | | | | |
| *Candida albicans* | 5 | 1 | | | 1 | | | 1 | | 1 | | |
| *Candida glabrata* | 5 | | | | | | | 1 | | | | |
| *Candida parapsilosis* | 5 | 1 | | | 1 | | | 1 | | | | |
| *Candida tropicalis* | 5 | | | | | | | 1 | | | | |
| *Cryptococcus neoformans* | 5 | | | | | | | 1 | | | | |
| *Cryptococcus laurentii* | 5 | | | | | | | 1 | | | | |
| *Acremonium* species | 6 | 1 | | | 1 | | | | | | | |
| *Aspergillus flavus* | 6 | | | | 1 | | | 1 | | 1 | | |
| *Aspergillus fumigatus* | 6 | 1 | | | 1 | | | 1 | | 1 | | |
| *Aspergillus glaucus* | 6 | | | | 1 | | | 1 | | 1 | | |

(continued)

**Table 3.1** (continued)

| Pathogens recovered from endophthalmitis | Clinical endophthalmitis types | | | | | | | | | | | Key |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Groups | Acute-onset postoperative (rate—.03–.2 %) | Bleb associated (rate—0.17–13.2 %) | Delayed-onset postoperative (rate—0.02 %) | Keratitis associated (rate—0.2 .4 %) | Post-intravitreal (rate—0.02–.09 %) | KPro-related rate (0–12 %) | Endogenous | Glaucoma drainage device (rate—0.11–0.5 %) | Trauma (rate—2–12 %) | | |
| *Aspergillus niger* | 6 | | | | 1 | | | 1 | | 1 | | |
| *Aspergillus terreus* | 6 | | | | 1 | | | 1 | | 1 | | |
| *Bipolaris* species | 6 | | | | 1 | | | | | | | |
| *Cladophialophora devriesii* | 6 | | | | | | | 1 | | | | |
| *Coccidioides immitis* | 6 | | | | | | | 1 | | | | |
| *Colletotrichum gloeosporioides* | 6 | | | | 1 | | | | | | | |
| *Curvularia* species | 6 | | | | 1 | | | | | | | |
| *Exserohilum* species | 6 | | | | | | | 1 | | | | |
| *Fonsecaea pedrosoi* | 6 | 1 | | 1 | | | | | | | | |
| *Fusarium* species | 6 | | | | 1 | | | 1 | | 1 | | |
| *Helicomyces* species | 6 | | | | | | | 1 | | | | |
| *Helminthosporium* species | 6 | 1 | | | | | | | | | | |
| *Histoplasma capsulatum* | 6 | | | | | | | 1 | | | | |
| *Lecythophora adecarboxylata* | 6 | | | | x | | | | | | | |
| *Lecythophora mutabilis* | 6 | | | 1 | x | | | | | | | |
| *Nocardia veterana* | 6 | | | | | | | 1 | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Paecilomyces lilacinus* | 6 | 1 | | | | | | 1 | | | | |
| *Paecilomyces* species | 6 | 1 | | | | | | 1 | | | | |
| *Paecilomyces variotii* | 6 | 1 | | | | | | 1 | | | | |
| *Phialemonium* species | 6 | | | | | | | 1 | | | | |
| *Phialophora verrucosa* | 6 | | | | | | | 1 | | | | |
| *Phialophora richardsiae* | 6 | | | | | | | 1 | | | | |
| *Sporothrix schenckii* | 6 | | | | | 1 | | | | | | |
| *Microsporidia* species | 7 | | | | | | | 1 | | | | |
| *Amoebae* | 7 | | | | | | | 1 | | | | |
| *Acanthamoeba* | 7 | | | | 1 | | | | | | | |
| | 141 | 62 | 23 | 15 | 34 | 43 | 7 | 65 | 11 | 33 | | |

Refs. [1–20], literature review and unpublished Bascom Palmer Eye Institute data

[a]All staphylococci other than *Staphylococcus aureus* are types of coagulase-negative staphylococci (some *Staphylococcus intermedius* strains are coagulase positive)

[b]Many of the streptococci listed are members of the viridans streptococcus group

of the *Streptococcus* genus recovered from endophthalmitis cases, causing 71 % of all streptococcal endophthalmitis cases in one large series [34]. Viridans streptococci are common causes of bleb-related, endogenous, and post-intravitreal injection endophthalmitis. Currently, the viridans streptococcus group contains 60 species and 12 subspecies [21, 32, 33]. The oral and nasal cavities of humans and animals are the most common reservoirs for this group. The viridans streptococci are also natural inhabitants of the gastrointestinal and female urogenital tract.

Several members of the Lancefield groups of streptococci such as groups A (*Streptococcus pyogenes*), B (*Streptococcus agalactiae*), C, and G are usually beta hemolytic and normally colonize humans (e.g., skin, oropharyngeal, gastrointestinal, vaginal), yet these groups are known for particularly virulent infections when they invade sterile sites. Animals including cats and dogs may also serve as reservoirs for colonization of human skin by various streptococci [32–35]. *Streptococcus pneumoniae* remains a frequent cause of acute endophthalmitis in patients with filtering blebs and may rarely cause acute-onset endophthalmitis after cataract surgery or intravitreal injections [34, 36, 37]. Enterococci were formerly classified as Lancefield group D streptococci, but these streptococcal-like bacteria now have their own genus, with two important species (*Enterococcus faecalis* and *E. faecium*). Vancomycin-resistant enterococci (or VRE) are mostly *E. faecium*.

### 3.2.3 Gram-Negative Bacteria

The *Enterobacteriaceae* (e.g., *Klebsiella*, *Serratia*, *Proteus*, *Escherichia coli*, *Enterobacter*) are the most frequently isolated gram-negative bacilli associated with endogenous endophthalmitis and can cause other types of endophthalmitis as well. *Klebsiella pneumoniae* is the most common cause of endogenous endophthalmitis in many East Asian nations. *Enterobacteriaceae* are normal inhabitants of the gastrointestinal tract of humans and warm-blooded animals [22, 24, 38–45].

Non-*Enterobacteriaceae* (*Pseudomonas*, *Haemophilus*, *Moraxella*) are infrequent endophthalmitis pathogens and are most often recovered from bleb-related or glaucoma drainage device-related endophthalmitis cases [13, 18, 46–50]. Others, *Stenotrophomonas maltophilia* [51, 52] and *Achromobacter xylosoxidans* [53], are emerging pathogens recalcitrant to commonly used intravitreal antibiotics.

### 3.2.4 Fungi

Fungi cause about 10 % of all endophthalmitis cases. Fungal pathogens, especially *Candida* species, are most often recovered from endogenous endophthalmitis cases but can be recovered from all types of healthcare- and community-acquired endophthalmitis [22, 54–57]. *Candida* species are the most common yeast pathogens [54, 58, 59]. A myriad of filamentous fungi (molds) have been recovered from endophthalmitis cases [60–62]. Molds may cause endogenous or exogenous

endophthalmitis (see Chaps. 10 and 11). *Aspergillus* species [54, 63] and *Fusarium* species [64–66] are the most commonly associated members.

### *3.2.5 Viruses and Protozoa*

Endophthalmitis is usually defined as an infection caused by bacteria or fungi, with intraocular infections due to viruses or protozoa included in the uveitis spectrum. However, the terminology may be changing, as new diagnostic techniques identify novel pathogens. The spectrum and frequency or the role viral pathogens play in healthcare- and community-acquired endophthalmitis is unknown. Routine viral cultures are rarely performed in the clinical microbiology laboratory. Members of the herpesvirus family have been recovered in culture from aqueous and vitreous fluids [67]. Increasingly, molecular techniques are being employed to detect the presence of viral DNA in intraocular samples [68–70]. The spectrum and diversity of involved pathogens are just emerging [71, 72].

Few protozoa are associated with infections of the aqueous or vitreous. Rare cases associated with endogenous infections (microsporidia) [73] or as an extension keratitis (*Acanthamoeba*) [74] have been described.

## 3.3 Role of the Microbiology Laboratory in Endophthalmitis

A clinical diagnosis of infectious endophthalmitis constitutes a medical emergency [1, 3]. The microbiology laboratory's role is to quickly confirm the clinical diagnosis to help guide the selection and administration of the most appropriate antimicrobial therapy. The need for microbial confirmation is expanding, with increasing reports of endophthalmitis associated with the rising number of intraocular surgeries, intravitreal injections, and corneal surgeries. Microbiological tools are evolving to accommodate the need by incorporating new, culture-dependent and culture-independent methods along with increased sensitivity for smears and other direct techniques.

Standard microbiological procedures which include smear preparation for specific stains and direct plate inoculation of select culture media are the most common and efficient diagnostic techniques for recovery of intraocular pathogens. Common smears and select media used for detection and recovery are outlined in Tables 3.2 and 3.3. The efficiency and relevancy of microbiology results is dependent on the quality and quantity of the specimen.

### *3.3.1 Specimen Collection and Processing*

Regardless of the precipitating event or category of endophthalmitis, specimen collection, processing, and interpretation remain the same. Aqueous and vitreous

**Table 3.2** Common stains for detecting and identifying ocular pathogens

| | |
|---|---|
| Gram stain | Stain to identify and characterize gram-positive versus gram-negative bacteria |
| Acid fast stains | Stain to identify and/or detect mycobacteria and *Nocardia* |
| Acridine orange | Fluorescent stain that interacts with microbial DNA and RNA. Rarely used in microbiology laboratories |
| Calcofluor white | Fluorescent stain that stains the chitin and cellulose of fungi, microsporidia, and *Acanthamoeba* |

**Table 3.3** Culture media for recovery and identification of common endophthalmitis pathogens

| | |
|---|---|
| 1 | Chocolate agar: An enriched medium for the recovery of fastidious organisms (i.e., *Neisseria gonorrhoeae* and *Haemophilus influenzae*) from clinical specimens. It is used as a general-purpose medium for the recovery of bacteria, yeasts, and molds from aqueous and vitreous fluids. It is the medium of choice for inoculation when fluid volume is limited. It must be placed in a $CO_2$ incubator, jar, or bag and incubated at 35 C for up to 7 days |
| 2 | 5 % Sheep blood agar: A general-purpose medium for the recovery of the most common bacterial and fungal endophthalmitis isolates. The pattern of hemolysis—complete (beta), partial (alpha), or none (gamma)—is documented using this media. It can be placed in an anaerobic environment for recovery of *P. acnes* and other anaerobes. For aerobes, it should be placed in the $CO_2$ incubator, jar, or bag at 35 C for up to 7 days. It can be kept in the anaerobic jar for 14 days |
| 3 | Thioglycollate broth: An all-purpose, enriched medium for the recovery of low numbers of aerobic or anaerobic (including *P. acnes*) organisms from ocular fluids and tissues. The broth dilutes out the effects of antibiotics and other inhibitory substances. It should be placed in the $CO_2$ incubator, jar, or bag at 35 C and kept for up to 21 days (*P. acnes*) |
| 4 | Anaerobic blood agar: A general, all-purpose medium for the recovery of anaerobic and facultative anaerobic organisms. This medium should be included for all chronic cases of endophthalmitis and/or where *P. acnes* is suspected. The viridians streptococcus group and beta hemolytic streptococci may grow better and faster on this plate. This medium is placed in an anaerobic jar or bag and incubated at 35 C for a minimal of 90 h and up to 21 days for *P. acnes* |
| 5 | Sabouraud agar: A selective medium used to promote the growth of fungi (yeasts and molds) from clinical specimens. Samples are incubated at 25 C for 1–2 weeks |
| 6 | Blood culture bottles: Contain specially prepared medium for the recovery of both aerobic and anaerobic bacteria and fungi. Intraocular fluids may be inoculated directly into blood culture bottles. Undiluted fluids should be inoculated into pediatric bottles and diluted fluids (6–12 mL of vitrectomy specimen) injected into a set of routine (adult) bottles. Bottles are incubated at 35 C and monitored daily manually or via automated blood culture machines |
| 7 | Lowenstein-Jensen medium is a selective medium for the recovery of acid-fast organisms (mycobacteria, *Nocardia*) from aqueous and vitreous fluids |
| 8 | CHROMagars—these are selective and differential chromogenic agars that can be used to simultaneously recover and differentiate staphylococci, enterococci, *Candida,* and some gram-negative pathogens directly from intraocular fluids or from colonies |

aspirate samples (0.3–1 cc) are collected by an experienced ophthalmologist using a needle and syringe. If samples are collected in a physician's office or an ambulatory center without access to fresh media, syringes *without needles* should be capped or the sample injected into a sterile 2-ml screw capped tube, which is placed into a plastic bag and then into a hard-sided, leakproof container for transport directly or

via courier to a microbiology laboratory. Syringes with needles, even if capped, should never be sent to a clinical laboratory. Some laboratories may not accept even capped needleless syringes due to the concern about the syringe plunger being pushed in inadvertently.

Vitrectomy samples are most often collected in the operating room. The vitrectomy debulks the microbial load and removes bacterial toxins and inflammatory mediates. The vitreous cassette and/or bag should be transported immediately to the microbiology laboratory for processing. Some surgeons prefer to collect a small sample of undiluted vitreous specimen directly into a 3-cc or 10-cc syringe before the infusion is turned on during vitrectomy.

## *3.3.2 Stains*

Dyes and of fluorochromes must be applied to view bacteria under the microscope. Stains and/or smears of intraocular fluids offer a rapid method for identification of the causative agent, type of inflammatory cells, and documentation of the presence of fibrin or fragmented lens material. The sensitivity of stains in detecting endophthalmitis pathogens is impacted by the quality of the sample, prior antibiotic treatment, and experience of microbiology personnel.

Stains should be prepared by placing a drop of intraocular fluid within a prescribed area on the slide. The fluid should not be spread, but left to air-dry. The type of stain performed is dependent on the suspected etiological agent.

### 3.3.2.1 Gram Stain

The Gram stain is the most frequently employed stain to screen intraocular fluids for the presence of microorganisms. It provides information on the bacterial morphology (round are cocci, rod shaped are bacilli) and cell wall content (gram positive or gram negative). The Gram stain can also reveal the presence of yeast and occasionally true hyphal elements and *Acanthamoeba* cysts.

Reagents include the primary stain (crystal violet), a mordant (iodine solution), a decolorizer (acetone plus alcohol), and a counterstain (safranin). Gram-positive organisms (e.g., staphylococci, streptococci, *Bacillus* species, *Propionibacterium* species) have cell walls made of a thick layer of peptidoglycan and retain the primary stain (crystal violet), so they appear blue or purple when viewed with the light microscope, while gram-negative bacteria (e.g., *Pseudomonas*, *Haemophilus*, *Moraxella*, *Serratia* species) have only a thin layer of peptidoglycan in their cell walls so do not retain crystal violet, but retain the counterstain safranin and appear pink or red. Yeasts retain the primary stain (blue-purple) and hyphae outer wall purple and cytoplasm pink. Most mold hyphae are poorly visualized by Gram stain.

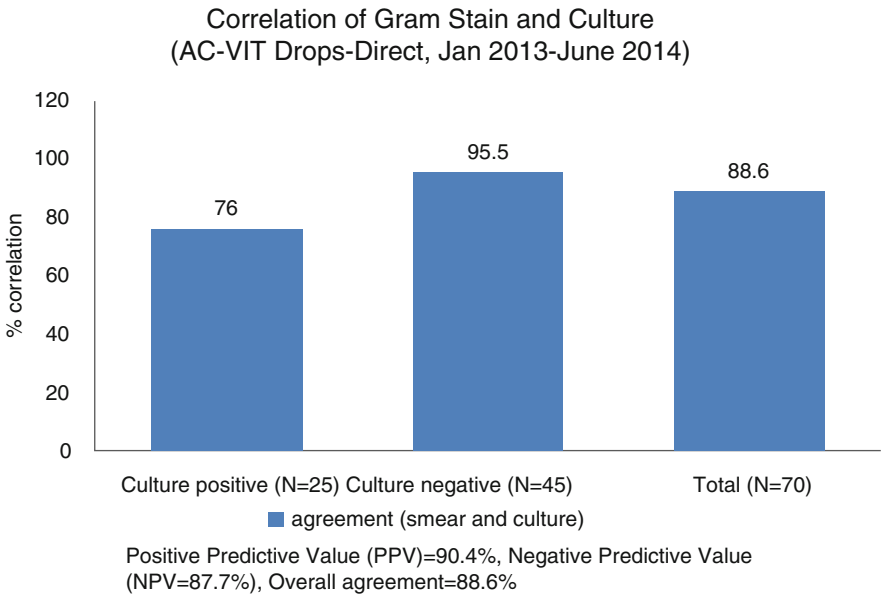


**Fig. 3.1** Correlation of Gram stain results and culture (*AC* anterior chamber, *VIT* vitreous sample)

Reported correlations of Gram stain with culture range from 16 to 88 % [4, 24, 25, 72, 75, 76]. In the European Society of Cataract & Refractive Surgeons (ESCRS) multicenter study of cataract surgery, there were 14 culture-positive cases of endophthalmitis [77]. In cases with both smear and culture available on aqueous (11 cases) or vitreous (10 cases), there was better concordance for vitreous Gram stains and cultures than for aqueous. Gram stains of aqueous were positive in 9 %, while corresponding aqueous cultures were positive in 64 %; vitreous Gram stains were positive in 70 %, while corresponding vitreous cultures were positive in 90 %. The sensitivity of Gram stain in detecting culture-positive intraocular infection was therefore 9 % for aqueous samples and 70 % for vitreous samples in this study. In relation to the final vitreous culture, Sharma et al. reported a sensitivity of 67 % and specificity of 84 % for Gram stains of culture-positive vitreous samples in a 1996 study of endophthalmitis [76]. Using three types of stains (Gram, Giemsa, or calcofluor) in a 2014 study, Sharma et al. reported that smear sensitivity was 67 % for culture-positive endophthalmitis cases that were caused by bacteria and fungi [25]. Data from our laboratory (Fig. 3.1) is consistent with these results. Gram stain correlation with culture was 76 % with a positive predictive value of 90 %.

### 3.3.2.2 Other Stains

Acid fast stains (Kinyoun stain (cold), Ziehl-Neelsen (hot), auramine-rhodamine (fluorescent)): The acid-fast stain is a differential stain used to identify or detect mycobacteria and/or other acid-fast microorganisms (*Nocardia*) in intraocular fluids. *Mycobacterium* species contain mycolic acids, waxes, and other lipids in the cell wall that retain or the carbol-fuchsin or fluorochrome stain and remain "acid fast" or resistant to decolonization with an acid alcohol.

Mycobacteria are infrequent intraocular pathogens, mainly occurring as an extension of keratitis or biomaterial-associated materials (i.e., glaucoma drainage implants, keratoprosthesis). Almost all mycobacterial endophthalmitis cases are due to atypical mycobacteria, which are environmental organisms.

Acridine orange is a fluorescent dye that intercalates into bacteria DNA (as well as host cells). Air-dried stains are flooded with acridine orange solution for 2 min and then gently washed. Organisms appear a bright orange against a green background when viewed under a fluorescent microscope. It is useful stain in highlighting and detecting the presence of bacteria and fungi in fluids such as the aqueous and vitreous where the microbial load might be quite low, but this stain is almost never used in clinical microbiology laboratories. There are no recent studies evaluating its use for intraocular. A study from 1985 comparing acridine orange to Gram stain for detecting bacteria in urine found that sensitivities were similar for the two stains [76A].

Calcofluor white is a fluorescent dye that binds cellulose and chitin in the cell walls of fungi, microsporidia, and *Acanthamoeba*. A fluorescent microscope is required for viewing the results of fluorescent stains.

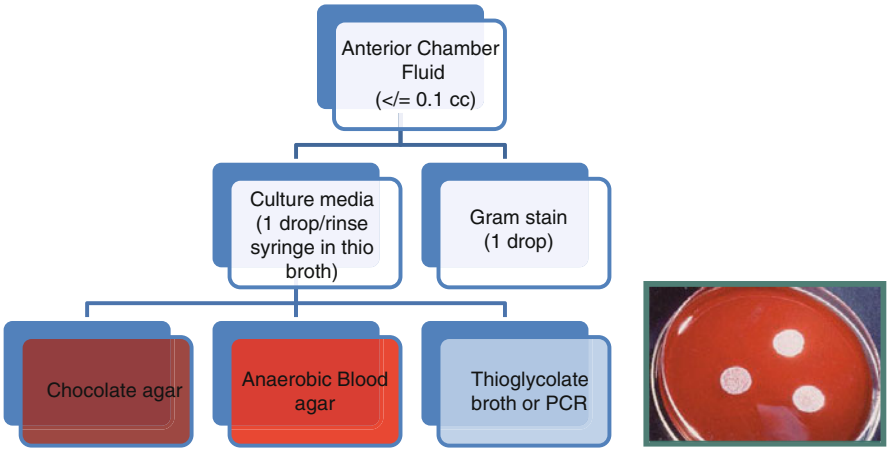


**Fig. 3.2** Direct plating scheme for aqueous paracentesis sample. Order of inoculation: chocolate agar > slide > thioglycollate broth > anaerobic blood agar

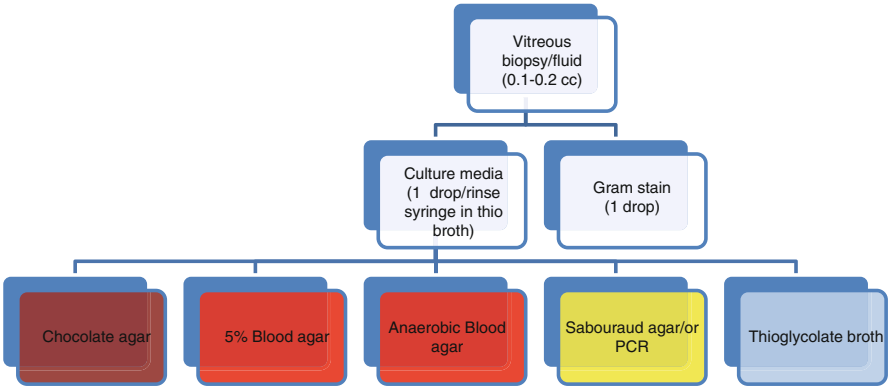


**Fig. 3.3** Direct plating scheme for undiluted vitreous sample. Order of inoculation: chocolate agar > slide > thioglycollate > anaerobic blood agar > Sabouraud/and aliquot for molecular testing

**Fig. 3.4** Direct plating scheme for diluted vitreous sample. Aliquots of 30–50 cc should be vacuumed filter through a 0.45 filter or centrifuged. Order of inoculation: chocolate > slide > Thioglycollate > anaerobic blood agar > sabouraud/ and aliquot for molecular testing

### *3.3.3 Culture Techniques*

Direct plating on select liquid and solid media is the most efficient method for simultaneous recovery and identification of bacteria and fungi from intraocular pathogens. Undiluted aqueous and vitreous samples should be inoculated directly onto a select panel of solid and liquid media and transported immediately or within 2 h to the microbiology laboratory. One drop of the collected fluid should be placed on a glass slide and air-dried prior to transport (Figs. 3.2 and 3.3).

The diluted vitreous samples must be concentrated using a ).45 filter and or centrifuged for 5 minutes at 3000 rpm (cytospin preparation). The 0.45 filter is sectioned and placed on select culture media and glass slides for stains as in Fig. 3.4.

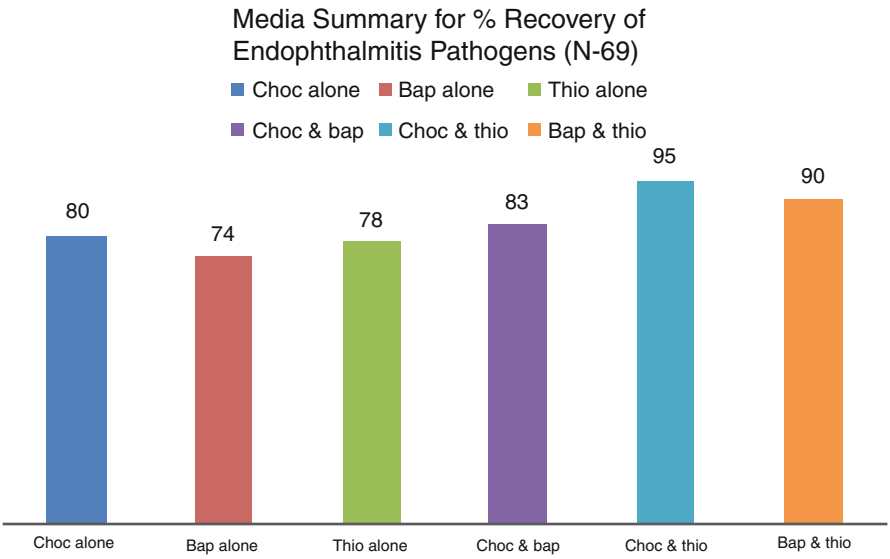


**Fig. 3.5** Efficacy of media for recovery of pathogens from intraocular fluids (*Key*: *choc* chocolate agar, *bap* 5 % sheep blood, *thio* thioglycollate broth)

The remaining filtered fluid can be used to set up viral cultures or frozen and saved for molecular studies.

Pellets from the centrifugation and/or cytospin preparations are distributed as for vitrectomy samples. After hours, aliquots from vitrectomy samples should be injected into pediatric (5 cc) and/or adult (10 cc) blood culture bottles, incubated at 35 C ± 2 C or at room temperature overnight, and transported to microbiology as early as possible the next day. Refrigeration may reduce microbial yield.

As in microbiology in general, the quality and relevance of the results for infectious endophthalmitis are dependent on the quality of specimen collection and transport. Culture-positive rates from postoperative endophthalmitis range from 10 to 70 % with the highest rates from traumatic cases [3, 78–81].

Spectrum and quantity of inoculated media is limited by collected volume. Protocols outline in Figs. 3.2, 3.3, and 3.4 may be modified when volume is limited.

Greater than 95 % of bacterial and fungal pathogens can be isolated with a combination of chocolate agar and thioglycollate broth and incubated at 35 C in $CO_2$ for a minimum of 5–7 days (Fig. 3.5). Approximately 90 % of gram-negative bacteria and streptococci will grow on media within 48 h, and many staphylococci will grow rapidly as well. Yeast and molds often grow more slowly.

Blood culture bottles offer a unique means of recovering ocular pathogens from dilute vitreous samples. Both bacteria and fungi can be recovered with sensitivities comparable to using the membrane filter or cytospin method for fluid concentration. Undiluted samples can be injected in pediatric bottles for enhanced recovery [82–84].

### *3.3.4 Pathogen Identification*

Rapid identification of recovered microorganism can help direct appropriate, early therapy and support infection control interventions. Tools for traditional microbial identification employ a combination of manual, phenotypic, automated, and molecular techniques and procedures for both bacteria and fungi.

Manual techniques include a battery of biochemical, enzymatic kits and specialized media that can identify many species of bacterial and yeast isolates within 4 h. Automated systems can provide rapid bacterial and yeast identification and susceptibilities with turnaround times ranging from 2 to 18 h.

#### 3.3.4.1 New Diagnostic Techniques

Ocular microbiology laboratories are beginning to evaluate new and emerging technologies developed for rapid organism recovery and identification directly from patient samples and/or culture media and how these might be employed to enhance recovery and identification of pathogens from intraocular fluids. These new diagnostic tests include 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 [3, 26, 57, 68, 72, 85–93].

These new methods may offer earlier and more accurate identification of staphylococci, *Candida,* and common enteric organisms. PCR and other molecular techniques for the identification of ocular pathogens in aqueous and vitreous samples are discussed in Chap. 4. Laboratories are using these techniques to increase pathogen detection and turnaround time.

Chiquet and colleagues compared PCR (16S eubacterial primers) and conventional methods of stains and culture for detection and recover microorganisms from dilute and undiluted vitreous fluids. The authors concluded that there was no significant difference between PCR and conventional tests for the detection of bacteria from dilute or undiluted vitreous [94].

Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) is a soft ionization process used in mass spectrometry to analyze biomolecules (proteins, nucleic acids). It offers the microbiology laboratory a rapid, accurate method for the identification of bacteria, fungi, and mycobacteria. Current drawbacks include limited database for fungi and some bacteria [93].

Peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) employs fluorescent-labeled probes to target and bind to species specific nucleic acid targets in bacteria and fungi. This technique can be used to identify common endophthalmitis-associated bacteria and yeast directly from the positive vitrectomy blood culture bottle with a turnaround time of 2 h or less [95].

Sakai and colleagues use DNA microarray to evaluate vitreous samples from 13 patients and found it complementary to culture and PCR for rapid confirmation of

endophthalmitis. DNA is a promising technique that can simultaneously detect multiple microbial and antibiotic genes [90].

### 3.3.5 *In Vitro Susceptibility Testing*

Both the in vitro susceptibility profile and the in vivo responses to commonly injected antibiotics are changing as pathogens become less susceptible to antibiotics. Isolates recovered from all cases of endophthalmitis should be evaluated for sensitivity to commonly injected intravitreal antibiotics (amikacin, ceftazidime, and vancomycin) using a minimal inhibitory concentration method (broth microdilution tests, Etests, or automated system) [75, 80, 96–103]. Disk diffusion may fail to detect heteroresistant populations (especially for vancomycin) that could contribute improper dosing and a more protracted clinical course [29, 79, 80, 98, 99, 101, 104, 105].

In general, 90 % of inciting bacterial pathogens are effectively killed and/or inhibited by the combination of the most commonly injected intravitreal antibiotics (ceftazidime and vancomycin). While greater than 98 % of gram-positive isolates remain susceptible to vancomycin, the vancomycin concentration necessary to inhibit or kill 90 % of the isolates is increasing. Resistance to amikacin and ceftazidime among gram-negative organisms commonly recovered in endophthalmitis (e.g., *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) is infrequent, but the rate of ceftazidime resistance in particular is increasing.

Cefuroxime is used as a prophylactic strategy in many European centers to prevent endophthalmitis after cataract surgery. However, in the 14 culture-positive endophthalmitis cases reported from the multicenter ESCRS trial of cefuroxime prophylaxis for cataract surgery, two of the six streptococcal species and three of the five *S. epidermidis* isolates were non-susceptible to cefuroxime. Overall, five of the 11 tested samples were cefuroxime non-susceptible [77].

Currently, there are no standards for correlation of in vitro susceptibility results with attainable intraocular antibiotic concentrations. The Clinical and Laboratory Standards Institute determines susceptibility breakpoints for each antibiotic-bacteria combination (e.g., oxacillin for staphylococci) based on the evaluation of systemic infections and achievable serum concentrations of systemically administered antibiotics. Correlation of in vitro results with clinical success in ocular infections, as in nonocular infections, is dependent on the mechanism of resistance and the pharmacokinetic dynamics of the host, drug, and infecting microorganism. Vitreous cultures remain positive in some patients even after appropriate intravitreal antibiotics have been given, so factors beyond in vitro susceptibility results play a role in determining the rate of intraocular sterilization by antibiotics in endophthalmitis.

The best management strategy for endophthalmitis is prevention. Rapid and early microbiological confirmation can improve management and contribute to better patient outcomes.

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# Chapter 4
# The Molecular Diagnosis of Endophthalmitis

**Christophe Chiquet, Sandrine Boisset, Pierre-Loïc Cornut, and Max Maurin**

## 4.1 Introduction

The incidence of acute postoperative endophthalmitis is low and varies depending on the type of eye surgery: approximately one case for every 1000–2000 cataract surgeries [1]. The causal infectious agent is a bacterium in most cases. Endophthalmitis requires rapid microbiological investigations to confirm the diagnosis and aggressive treatment, including intravitreal administration of antibiotics and in 30–60 % of patients a therapeutic vitrectomy. Identification of the microorganism involved is important for several reasons: to quickly confirm the infectious nature of inflammation, to justify and adapt the intravitreal antibiotic therapy, to rationalize the surgical decision for therapeutic vitrectomy, to precisely determine the epidemiology of the disease, and to reevaluate surgical hygienic procedures. While the clinical criteria for diagnosis of endophthalmitis have not evolved in recent years (decreased visual acuity in an inflamed and often painful eye), the microbiological diagnosis has benefited from advances in molecular biology techniques allowing rapid detection and identification of human pathogens.

C. Chiquet, MD, PhD (✉)
Department of Ophthalmology, Grenoble Alpes University, Grenoble, France

Department of Ophthalmology, University Hospital of Grenoble, Grenoble, France
e-mail: christophe.chiquet@inserm.fr

S. Boisset, PharmD, PhD • M. Maurin, MD, PhD
Department of Microbiology, Grenoble Alpes University, Grenoble, France

Department of Microbiology, University Hospital of Grenoble, Grenoble, France

P.-L. Cornut, MD, PhD
Department of Ophthalmology, University of Lyon, Lyon, France

Department of Ophthalmology, University Hospital, Lyon, France



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### *4.1.1 Intraocular Samples*

#### 4.1.1.1 Sample Collection

Intraocular samples, i.e., aqueous and vitreous, must be obtained after local antisepsis. The French Institutional Endophthalmitis Study (FRIENDS) group recently reported that pan-bacterial polymerase chain reaction (PCR) testing (i.e., 16S rRNA gene amplification and sequencing) has comparable sensitivity when testing diluted or undiluted vitreous [2]. Collecting diluted vitreous is easier to perform and does not induce hypotony, therefore limiting the risk of choroidal hemorrhage, retinal detachment, or displacement of the infusion cannula (as compared with undiluted vitreous sampling).

#### 4.1.1.2 Sample Processing and Storage

The sample collected for PCR testing should be placed in a sterile screw-capped DNA-free tube. The minimum volume for molecular analysis is approximately 50 µl. This tube should be placed in a secondary sterile container. The delivery time of the sample to the microbiology laboratory must be as short as possible and should not exceed 2 h at room temperature. If these conditions cannot be fulfilled, the PCR tubes should be stored at 4 °C for 48 h or −20 °C for longer periods [3].

### *4.1.2 Molecular Techniques for the Diagnosis of Endophthalmitis*

In recent years, a number of PCR-based assays have been implemented in microbiology laboratories for routine diagnosis of infectious diseases. Although the culture methods remain the gold standard because of their high specificity and the possibility to test the susceptibility of isolated pathogens to antibiotics, their sensitivity may be low, especially for fastidious and slow-growing microorganisms. In endophthalmitis patients, molecular methods provide a more rapid and sensitive diagnosis [4–6]. PCR-based techniques may also be used to detect viral or fungal nucleic acids (DNA or RNA) [7, 8].

PCR amplification of DNA usually requires three steps: total DNA extraction from clinical samples, target DNA amplification using specific primers, and a post-PCR step to identify the amplified products (Fig. 4.1). Steps 2 and 3 are combined for real-time PCR, reducing the turnaround time of the procedure (60–90 min versus 120–180 min). Whatever DNA amplification method is used, a number of controls are needed to ensure the accuracy of the results, including a DNA extraction control (proper DNA extraction), a negative amplification control (no false-positive results), a positive amplification control (no false-negative results), and an internal control (no DNA polymerase inhibitors). It should be mentioned that many PCR tests use

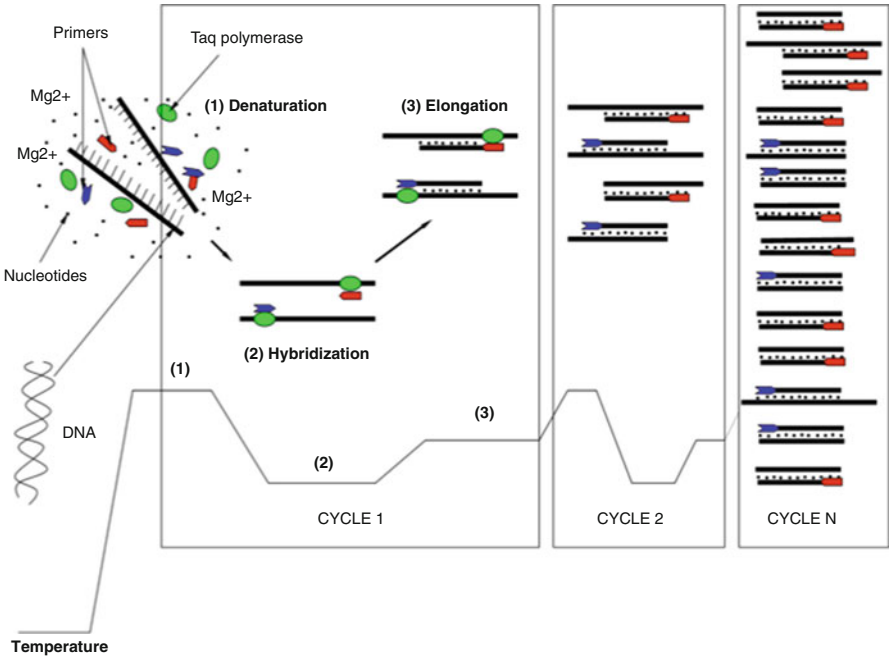


**Fig. 4.1** Principle of the polymerase chain reaction (PCR) assay

amplification of the human β-globin gene present in all eukaryotic cells as a specific internal control, but this may not be appropriate for intraocular samples, which often contain few eukaryotic cells. It should also be emphasized that molecular diagnostic tools currently available in clinical laboratories for etiological diagnosis of endophthalmitis are often made in-house and thus require careful validation prior to their clinical use. Development of a few commercial tests would be useful for the molecular diagnosis of endophthalmitis.

#### 4.1.2.1 Pan-bacterial Conventional PCR

This technique is based on amplification of the 16S rRNA gene (encoding the small subunit of bacterial ribosomal DNA) using universal primers complementary to DNA regions that are conserved among almost all bacterial species (Fig. 4.2). The use of pan-bacterial PCR for aqueous and vitreous humors has been described by several authors [4, 9–11]. Conventional PCR is typically used for amplification of the 16S rDNA. A precise identification of the bacterial species involved requires a post-PCR step, which often corresponds to the sequencing of the amplified DNA (Fig. 4.3) and its comparison to DNA sequences contained in large databases (e.g., GenBank). This step uses DNA sequence alignment programs such as the BLASTN program of the National Center of Biotechnology Information (NCBI, USA,

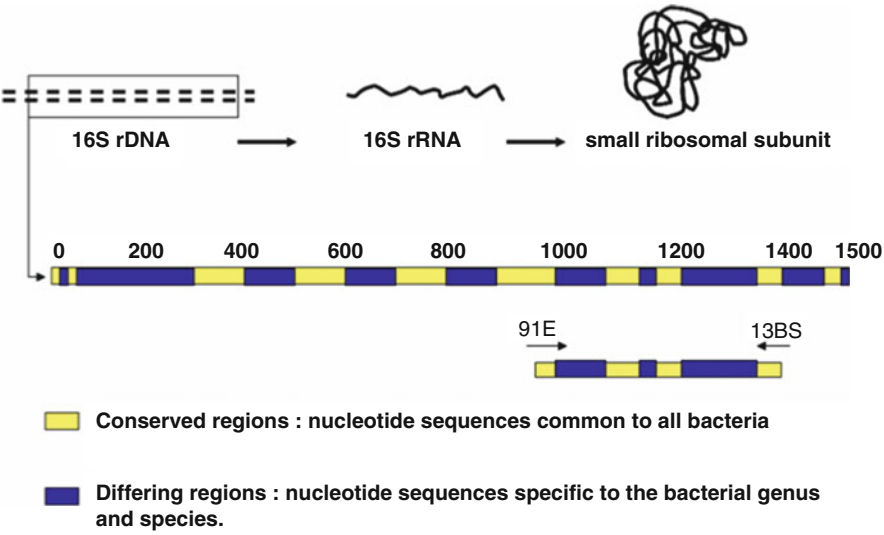


**Fig. 4.2** Scheme of the 16S rRNA gene (1500 nucleotides). Conserved nucleotide sequences in Eubacteria alternate with variable nucleotide sequences specific for bacterial genera or species

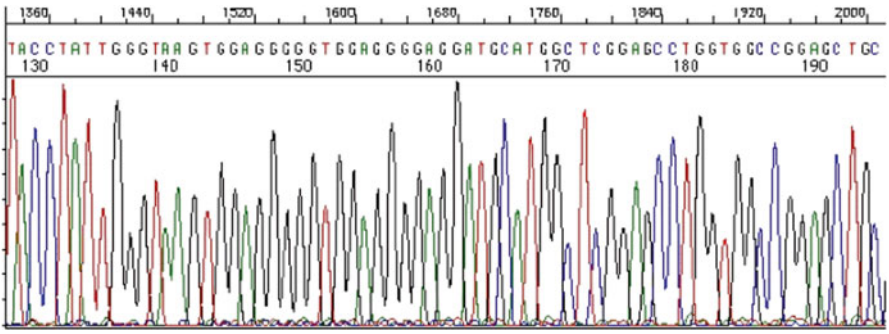


**Fig. 4.3** DNA sequencing: chromatogram obtained using an automated DNA sequencing procedure. Each DNA fragment is complementary to the target DNA and contains a nucleotide labeled with a specific fluorophore for each nucleotide type (A, T, C, or >G). These fragments are separated using acrylamide gel electrophoresis, with subsequent detection of the terminal labeled nucleotide

http://blast.ncbi.nlm.nih.gov/) or phylogenetic programs (e.g., Quick BioInformatic Phylogeny of Prokaryotes, Lyon University, France, http://umr5558-sud-str1.univ-lyon1.fr/lebibi/lebibi.cgi) [4, 11–15]. The QBPP (formerly BIBI) software was designed to automate DNA sequence analysis for bacterial identification in the clinical field. Species identification is considered to be reliable when the percentage of similarity between the analyzed 16S rDNA sequence and the sequences deposited in databanks is at least 98 % [16]. A phylogenetic approach (Fig. 4.4) is now often used [16, 17].

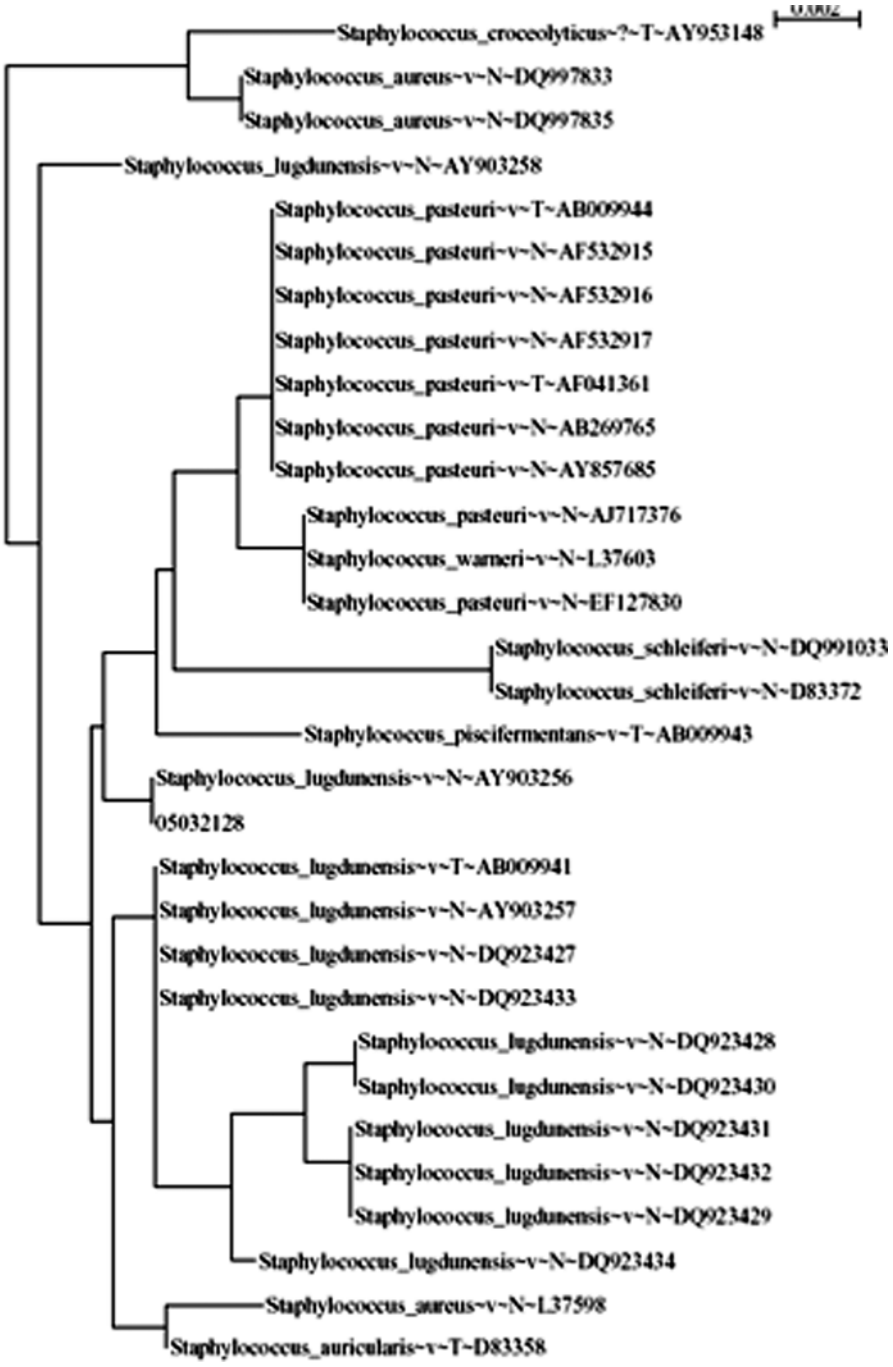


**Fig. 4.4** A phylogenetic tree obtained after DNA sequence alignment and analysis and determination of a sequence similarity index

The use of alternative methods to DNA sequencing is now much less common. The amplified DNA may be hybridized with a fluorophore-labeled probe, which can specifically identify a bacterial group (e.g., gram-positive or gram-negative bacteria), a bacterial genus, or a bacterial species [18–20]. Pan-bacterial PCR may be followed by a "nested PCR" (see below) using specific primers to quickly distinguish gram-positive from gram-negative bacteria [10, 18, 19]. Restriction fragment length polymorphism (RFLP) methodology is based on the use of restriction enzymes that cut DNA at specific sequences (restriction sites). The resulting DNA fragments are then separated by gel electrophoresis, and species identification is based on specific restriction patterns [15].

Pan-bacterial PCR has the advantage of covering the entire bacterial spectrum. It is particularly useful when a large panel of bacterial species may cause the same disease, such as in endophthalmitis patients. The limitations of this technique include lower sensitivity and specificity as compared to species-specific PCR and more importantly a long turnaround time (2–3 days is required for species identification). The sensitivity can be slightly improved by performing a second round of PCR amplification using amplified products obtained after the primary PCR reaction. This technique, referred to as nested PCR, significantly increases the risk of false-positive results due to exogenous DNA contamination. Different species may share similar 16S rDNA sequences (e.g., *Streptococcus mitis* and *Streptococcus pneumoniae*), and their differentiation requires further identification tests [21]. False-positive results may occur due to contamination of clinical samples with exogenous DNA. The pan-bacterial PCR assay is mainly useful when infection is caused by a single bacterial species, which is often the case in endophthalmitis patients.

For samples with a polymicrobial flora, the mixture of 16S rDNA sequences obtained is more difficult to analyze. In this case, amplified DNA from PCR reactions must be cloned into a plasmid to aid sequencing and to establish the identity of individual PCR products in samples with mixed populations of 16S rDNA [15]. This technique is tedious and rarely performed on a routine basis.

Finally, antibiotic susceptibility testing of the bacteria involved requires their isolation in culture. Only a few resistance gene determinants can be detected using PCR.

It should be noted that a similar procedure may be implemented for fungal pathogens, by amplification and sequencing of the 18S rRNA or 28S rRNA coding genes (fungal ribosomal RNA molecules). This diagnostic approach, which can be referred to as the pan-fungal PCR, is less commonly used than for the detection of bacteria [8, 22]. Fungal PCR assays are more prone to giving false-positive results than bacterial assays because of an increased risk of exogenous contamination and therefore may be more difficult to interpret.

#### 4.1.2.2 Pan-bacterial Real-Time PCR

Recent studies have reported the use of real-time PCR rather than conventional PCR for rapid detection of bacterial 16S rDNA [11, 20, 23]. Real-time PCR combines a PCR amplification of target DNA with simultaneous detection of the amplified PCR products using fluorescent reporter molecules, which may be dyes that bind to the

double-stranded DNA (e.g., SYBR® Green) or sequence-specific probes (e.g., TaqMan® Probes). The PCR amplification process can be monitored in real time by measuring the progressive increase in the fluorescence emitted by the reporter molecules. This process has a shorter turnaround time than conventional PCR because it eliminates the postamplification step.

The real-time PCR technology may also be used for rapid detection and differentiation of large groups of microorganisms. Bispo et al. [24] described two coupled real-time PCR reactions for the detection and differentiation of gram-positive and gram-negative bacteria causing endophthalmitis.

#### 4.1.2.3 Specific PCR and Real-Time PCR

Specific and real-time PCR tests have been developed for the detection of specific pathogens. While the PCR technique uses pathogen-specific primers (complementary to a specific region of the target pathogen), most real-time PCR tests also include specific probes, increasing the specificity of detection and identification of the target microorganisms. Specific real-time PCR tests are also easier to implement in clinical microbiology laboratories and are usually more rapid and sensitive than PCR assays [20]. Both techniques may allow the detection of a specific bacterial genus or species (e.g., all *Staphylococcus* species or *Staphylococcus aureus*, respectively).

The main drawback of specific PCR or real-time PCR methods is the need for oriented diagnosis (a priori search for a bacterium). Therefore, these tests are usually combined with pan-bacterial PCR testing. In endophthalmitis patients, real-time PCR assays are mainly used for early detection of the most virulent species (e.g., *S. aureus* and *S. pneumoniae*) and fastidious or slow-growing species. As an example, Therese et al. developed a specific PCR targeting *Propionibacterium acnes* [25].

#### 4.1.2.4 Multiplex PCR and Real-Time PCR

To enhance the cost effectiveness ratio of the molecular tests, a rational approach would be the use of multiplex PCR or real-time PCR, which are variants of these techniques allowing simultaneous detection of multiple DNA targets in a single reaction. Goldschmidt et al. [20] reported the use of a multiplex real-time PCR assay allowing simultaneous detection of several genera (*Staphylococcus*, *Streptococcus*, *Haemophilus*, *Pseudomonas*, *Acinetobacter*, *Corynebacterium*) and families (*Enterobacteriaceae* and *Propionibacteriaceae*).

#### 4.1.2.5 Quantitative Real-Time PCR

When using real-time PCR technology, a threshold cycle can be determined as the number of amplification cycles required for the fluorescent signal to cross a predefined threshold. Using a calibration curve, the threshold cycle can give an estimation of the amount of target DNA present in the clinical sample before amplification.

Sugita et al. [11, 26] used quantitative real-time PCR to diagnose bacterial endophthalmitis. They detected a high number of bacterial genome units in ocular samples (from $1.7 \cdot 10^3$ to $1.7 \cdot 10^9$ genome units/ml). Determination of the bacterial load in intraocular samples could help differentiate true infection from exogenous contamination when samples are collected. Melo et al. [27] defined a cutoff threshold cycle differentiating infection from contamination, by testing intraocular samples from patients with proven bacterial endophthalmitis and aqueous samples obtained at the end of cataract surgeries taken as controls. Using a broad-range PCR, a threshold cycle value between 19.5 and 34.5 was compatible with bacterial endophthalmitis, while a threshold cycle value of 39 was found for the two contaminated aqueous humor samples.

#### 4.1.2.6 Reverse Transcriptase PCR (RT-PCR)

In the reverse transcriptase assay, DNA amplification by PCR is preceded by a reverse transcription reaction in order to produce complementary DNA from RNA. Bacterial mRNAs have been proposed as markers for cell viability since they are very unstable molecules with very short half-lives inside the cell. Thus, the detection of mRNAs indicates that the bacterium is alive and metabolically active. Aarthi et al. [28] developed an RT-PCR assay targeting the 16S rRNA to determine the bacterial viability in intraocular specimens.

#### 4.1.2.7 DNA Microarray

DNA microarray analysis is a molecular method that simultaneously detects and identifies a wide variety of genes in a single experiment. In the study conducted by Sakai et al., 76 pathogen-specific probes were fixed on a chip to hybridize labeled PCR products amplified from clinical samples. This microarray assay, previously developed to detect and identify 76 bloodstream infection-associated pathogens (bacteria and fungi) in blood samples, was applied to ocular samples collected from patients with clinically diagnosed endophthalmitis [29]. The main drawback of this technology is that a limited number of microarray assays for diagnostic purposes are commercially available, and these tests are usually very costly.

### *4.1.3 Contribution of PCR-Based Assays to the Diagnosis of Postoperative Endophthalmitis*

In patients with acute postoperative bacterial endophthalmitis, gram-positive bacteria are predominant: 85 % of the microorganisms involved in the French GEEP study (group of epidemiologic and prophylactic studies) [30], 94.1 % in the American Endophthalmitis Vitrectomy Study [31–33], and 97 % in the French

multicenter study of the FRIENDS group [4]. Among these gram-positive bacteria, *Staphylococcus epidermidis* predominated (45–50 %), followed by streptococci (24–37.7 %) and *S. aureus* (7.5–11.5 %) [4]. Gram-negative bacteria (e.g., *Escherichia coli*, *Proteus*, *Klebsiella*, *Serratia*, and *Pseudomonas* species) account for 3–15 % of culture-positive endophthalmitis cases [4, 30]. Polymicrobial infections have been described in several studies, with a frequency varying from 0 to 29 % [34, 35]. In our experience, coinfection is rare in this type of endophthalmitis.

The use of PCR for microbiological diagnosis of endophthalmitis was first reported in 1994 [36]. The studies published since 1994 are summarized in Table 4.1. They show that molecular biology techniques are useful for diagnosis of acute [4, 10, 11, 13, 18–20, 23, 25, 38] and chronic endophthalmitis [14, 19, 23, 25, 36, 38].

Most of the studies published have used conventional pan-bacterial PCR [13, 15, 19, 25, 36–38] (Table 4.1). Identification of the genus and species from conventional pan-bacterial PCR has not been systematically reported [25, 36–38]. When identification was attempted, in most studies this post-PCR stage was performed by sequencing [10, 13–15], more rarely using restriction fragment length polymorphism (RFLP) [15], gram-positive/gram-negative nested PCR [19], or hybridization of specific gram-positive/gram-negative waves [18]. In a recent review [41], we reported that an analysis from 16 studies shows a 40.5 % identification rate for conventional culture (193 positive samples out of 476) and 82.3 % for PCR (451/548 positive samples); the number of false-positives remains very low, limited to 3 % (9/296 control samples).

The FRIENDS group reported the sensitivity of pan-bacterial PCR in 100 acute endophthalmitis cases following cataract surgery; for aqueous samples, this sensitivity was similar to that of conventional culture (35 % versus 38 %) [4]. However, the combination of the two techniques allowed identification of a bacterial species in 47 % of cases. The identification rate increased to 68 % for vitreous samples when combining PCR and culture, while comparable sensitivity values were found for culture (54 %) and PCR (57 %) alone. When all of clinical samples were considered, pan-bacterial PCR was positive in 87 % of patients, and 25 % of patients had a positive PCR test but negative cultures. In addition, if the results of cultures were not taken into account, PCR only would have made the diagnosis in 61 % of the cases. Thus, pan-bacterial PCR and traditional cultures are actually complementary diagnostic methods for the etiological diagnosis of postoperative endophthalmitis. Pan-bacterial PCR had much higher sensitivity than culture when vitreous samples were collected following one or more intravitreal injections of antibiotics (70 % versus 9 % sensitivity, respectively) [4]. Additionally, pan-bacterial PCR has the same sensitivity for diluted vitreous than for undiluted vitreous samples collected during pars plana vitrectomy [2]. Results of the FRIENDS group study also indicated that, for a given patient, there was no need to repeat bacteriological analyses if PCR and culture testing of the first collected intraocular samples were both negative.

Broad-range real-time PCR for bacteria measures the amplification of the target rDNA genes [11]. This technique provided a diagnosis in 64 % of the cases. Since this PCR allows quantification of bacterial load, it can be used to distinguish contamination and infection on cycle threshold values [27].

**Table 4.1** Results of major studies using PCR in endophthalmitis

| Study | Population studied, samples/ infection category | Technique | Results |
|---|---|---|---|
| Hykin et al. [36] | 19 patients<br>19 chronic postoperative endophthalmitis<br>23 samples (V from PPV)<br>29 negative controls (V) | Phenol chloroform DNA extraction<br>*Nested PCR* with 16S rDNA primers, *no sequencing mentioned* | Culture +: 39 % (9/23)<br>16S rDNA PCR +: 74 % (17/23)<br>16S rDNA PCR + for controls: 14 % (4/29)<br>Sensitivity of the 16S rDNA primers: 50 fg (approximately 10 genome copies) of *S. epidermidis*<br>*P. acnes* PCR + in vitreous: 35 %<br>*P. acnes* PCR + in controls: 0 % |
| Lohman et al. [10] | 16 patients<br>10 acute and 6 chronic postoperative endophthalmitis<br>32 samples (16 A, 16 V from PPV)<br>20 controls (10 A, 10 V) | DNA extraction with QIAamp tissue kit (Qiagen)<br>*PCR sequencing, hybridization with probes specific for gram + and –* | Culture +: 25 % (8/32)<br>In A: 6.2 % (1/16); in V: 43.7 % (7/16)<br>16S rDNA PCR +: 93.7 % (30/32)<br>In A: 100 % (16/16)<br>In V: 87 % (14/16, negative in 2 chronic cases)<br>Correlation with culture: 100 % for positive results<br>16S rDNA PCR + in controls: 0 % |
| Therese et al. [25] | 55 patients<br>Acute and chronic, exogenous and endogenous, bacterial and fungal endophthalmitis<br>58 samples: 28 A, 30 V from PPV)<br>20 controls (6 A, 14 V) | Phenol chloroform DNA extraction<br>*Nested PCR, no sequencing mentioned 16S rDNA primers*<br>*Nested PCR with P. acnes-specific primers* | Culture +: 46.5 % (27/58) (20 bacteria and 7 fungi)<br>16S rDNA PCR +: 63.8 % (37/58)<br>16S rDNA PCR + in controls: 5 %<br>Sensitivity of the 16S rDNA PCR: 1 pg after round 1, 40 fg after round 2<br>*P. acnes* PCR +: 52.9 % (9/17 16S rDNA PCR + with culture – samples)<br>*P. acnes* PCR + in controls: 0 %<br>Sensitivity of the *P acnes* primers: 1 pg after round 1, 50 fg after round 2 |

| | | | |
|---|---|---|---|
| Okhravi et al. [15] | 25 patients<br>37 samples (15 A, 22 V)<br>38 controls (19 A, 19 V) | Phenol chloroform DNA extraction<br>*Nested PCR, bacterial identification by RFLP and DNA sequencing*<br>*Cloning and sequencing for polymicrobial infection* | Culture +: 54 % (20/37)<br>In A: 33 % (5/15); in V: 68 % (15/22)<br>16S rDNA PCR +: 100 % (37/37)<br>Correlation with culture: 100 % for positive results<br>6 unidentified rDNA sequences due to poor sequence quality or polymicrobial infection<br>16S rDNA PCR + in controls: 5 % (2/38, 1 A, 1 V) |
| Anand et al. [18] | 55 patients<br>29 postoperative (16 acute, 13 delayed), 22 post-traumatic, 4 endogenous endophthalmitis<br>57 samples (17 A, 40 V)<br>25 controls (10 A, 15 V) | Phenol chloroform DNA extraction<br>*Conventional PCR, hybridization with gram + and gram − probes* | Culture+: 56.1 % (32/57)<br>In A: 47 % (8/17); in V: 60 % (24/40)<br>16S rDNA PCR +: 91.2 % (52/57)<br>In A: 88 % (15/17; 5 g+ and 10 g−)<br>In V: 92 % (37/40; 19 g+ and 20 g−)<br>Correlation with culture: 100 % for positive results<br>2 vitreous samples positive for both gram+ and gram−<br>Sensitivity of the PCR-DNA probe hybridization evaluated on a range of common pathogens: 30 fg of DNA<br>16S rDNA PCR + in controls: 0 % |
| Lohmann et al. [14] | 25 patients<br>Chronic post-cataract endophthalmitis<br>50 samples (25 A, 25 V)<br>20 controls (10 A, 10 V) | DNA extraction: QIAamp tissue kit (Qiagen)<br>*PCR sequencing*<br>*16S rDNA primers and pan-fungal primers* | Culture +: 12 % (6/50)<br>In A: 0 % (0/25); in V: 24 % (6/25)<br>16S rDNA PCR +: 88 % (44/50)<br>In A: 84 % (21/25); in V: 92 % (23/25)<br>16S rDNA PCR + in controls: 0 % |
| Bagyalakshmi et al. [37] | 30 patients<br>Post-cataract (acute 9, chronic 3), post-trauma (1), endogenous (1) endophthalmitis<br>30 samples (19 A, 11 V)<br>Comparative results of the different methods available in 14 samples (8 A and 6 V) | DNA extraction: Qiagen kit<br>*Nested–multiplex PCR*<br>*16S rDNA primers, P. acnes primers, pan-fungal primers*<br>For pan-bacterial and *P. acnes* PCR, a second PCR was performed (nested PCR) | Culture +: 21.5 % (3/14)<br>In A: 25 % (2/8); in V: 16.7 % (1/6)<br>16S rDNA PCR +: 85.7 % (12/14)<br>In A: 87.5 % (7/8); in V: 83.3 % (5/6)<br>Pan-fungal PCR +: 14.3 % (2/14, 2 samples 16S rDNA PCR −)<br>*P. acnes* PCR +: 28.6 % (4/14)<br>Sensitivity of the multiplex PCR for detection of eubacterial and *P. acnes* genome: 100 fg |

(continued)

**Table 4.1** (continued)

| Study | Population studied, samples/ infection category | Technique | Results |
|---|---|---|---|
| Chiquet et al. [12] | 30 patients<br>Acute and delayed-onset endophthalmitis<br>44 samples (28 A, 16 V from PPV)<br>40 controls (30 A, 10 V) | DNA extraction with Qiagen kit<br>*PCR sequencing*<br>*16S rDNA primers*<br>*91E*: *TCAAAKGAATTGACGGGGGC*/*13BS*: *GCCCGGGAACGTATTAC* | Culture +: 31.8 % (14/44)<br>In A: 39.3 % (11/28); in V: 18.7 % (3/16)<br>16S rDNA PCR +: 61.4 % (27/44)<br>In A: 60.7 % (17/28); in V: 62.5 % (10/16)<br>Correlation with culture: 100 % for positive results<br>Sensitivity of the PCR for detection of *S. epidermidis* genome: 500–1000 pathogens<br>Culture or 16S rDNA PCR + in controls: 0 % |
| Chiquet et al. [4] | 100 patients<br>Acute post-cataract endophthalmitis<br>246 samples<br>114 initial samples (IS) collected before intravitreal antibiotics (76 A, 38 V from biopsy)<br>132 secondary samples (SS) after intravitreal antibiotics (62 A, 70 V from biopsy or PPV)<br>60 controls (35 A, 25 V) | DNA extraction with Qiagen kit (Qiagen)<br>*PCR sequencing*<br>*16S rDNA primers* | Culture +: 43.7 % (45/103) in IS; 12.6 % (15/119) in SS<br>In A: 38.2 % (26/68) in IS; 19.6 % (10/51) in SS<br>In V: 54 % (19/35) in IS; 7.3 % (5/68) in SS<br>16S rDNA PCR +: 41.9 % (47/112) in IS;<br>54 % (67/124) in SS<br>In A: 34.6 (26/75) in IS; 29 % (16/55) in SS<br>In V: 56.7 % (21/37) in IS; 73.9 % (51/69) in SS<br>Correlation with culture: 100 % for positive results<br>Culture or 16S rDNA PCR + in controls: 0 % |
| Sowmya and Madhavan [38] | 72 patients<br>45 post-cataract (21 acute, 14 delayed, 10 chronic), 16 post-trauma, 11 endogenous endophthalmitis<br>144 samples (72 A, 72 V), intravitreal antibiotics before sampling in most cases | DNA extraction: AccuPrep® Genomic DNA extraction kit (Bioneer)<br>*Nested PCR*, *no sequencing mentioned*<br>16S rDNA primers | Culture +: 37.5 % (27/72 patients) 24 bacteria and 3 fungi<br>16S rDNA PCR +: 84 % (121/144 samples) (corresponding to 100 % of patients, 24 polymicrobial cases with mixed sequences)<br>In A: 77.7 % (56/72); in V: 90.2 % (65/77) |

| | | | |
|---|---|---|---|
| Goldschmidt et al. [20] | 20 patients<br>20 samples (10 A, 10 V)<br>10 controls (5 A, 5 V) | DNA extraction: MagNA PureNucleic Acid isolation kit (Roche)<br>*Real-time multiplex PCR with universal primers and specific probes* for genera *Staphylococcus*, *Streptococcus*, *Haemophilus*, *Pseudomonas*, *Enterobacteria*, *Acinetobacter*<br>*16S rDNA primers*<br>For *Corynebacterium* and *Propionibacterium*, original sets of primers and probes were designed | Culture +: 75 % (15/20)<br>In A: 80 % (8/10) including 1 yeast<br>In V: 70 % (7/10) including 1 *Aspergillus*<br>16S rDNA PCR +: 95 % (19/20)<br>In A: 100 % (10/10)<br>In V: 90 % (9/10)<br>Correlation with culture-positive results in all cases except one: culture positive for yeast and PCR positive for *Enterobacteria*<br>Sensitivity of real-time PCR 0.01 CFU of Bac/µl<br>Control samples were negative |
| Sugita et al. [11] | 19 patients<br>10 postoperative (6 acute, 4 delayed), 1 post-traumatic, 5 endogenous, 2 keratitis, 1 post-intravitreal injection endophthalmitis<br>19 samples (8 A, 11 V)<br>15 controls | DNA extraction: DNA mini kit (Qiagen)<br>*Quantitative real-time PCR assay (TaqMan technology)*<br>*16S rDNA primers*<br>*PCR sequencing in samples with high amounts of DNA (n=9/19)*<br>*16S rDNA primers* | Culture +: 53 % (10/19)<br>In A: 50 % (4/8); in V : 55 % (6/11)<br>16S rDNA PCR +: 95 % (18/19)<br>In A: 88 % (7/8); in V: 100 % (11/11)<br>Correlation with culture: 100 % for positive results<br>Detection limit of the TaqMan RT-PCR for detection of *S. aureus* genome: 10 copies<br>Control samples were negative |
| Bispo et al. [24] | 14 patients<br>12 postoperative (11 acute, 1 acute delayed onset); 2 endogenous endophthalmitis<br>21 samples (10 A, 11 V)<br>62 controls (50 A, 12 V) | DNA extraction: QIAamp DNA mini kit (Qiagen)<br>*Real-time SYBR Green PCR followed by sequencing*<br>*16S rDNA primers*<br>*Multiplex real-time PCR with one gram + specific TaqMan probe and one gram − specific TaqMan probe* | Culture +: 47.6 % (10/21)<br>In A: 40 % (4/10); in V: 54.5 % (6/11)<br>16S rDNA PCR +: 95.3 % (20/21) including 6 mixed sequences<br>In A: 100 % (10/10); in V: 90.9 % (10/11)<br>Four samples showed a mixed amplification signal for gram classification<br>Correlation with culture: 100 % for positive results<br>Detection threshold for *S. epidermidis* was 100 fg/µl with pan-bacterial PCR and 1 pg/µl with gram + specific PCR<br>16S rDNA PCR false-positive rate in controls: 3.2 % (4 % in A, 0 % in V) |

(continued)

**Table 4.1** (continued)

| Study | Population studied, samples/ infection category | Technique | Results |
|---|---|---|---|
| Melo et al. [27] | 11 patients with acute postoperative endophthalmitis<br>9 V, 7 A<br>12 control V, 50 control A | *SYBR Green 16S rDNA-based universal PCR*<br>Gram discrimination by a *multiplex Gram-specific TaqMan-based PCR* | Positivity of real-time PCR in 91 %<br>The cycle threshold cutoff value was 36 for universal PCR (sensitivity 94 %, specificity 100 %) and 38 for Gram-specific PCR (Se 94 %, Sp 100 %)<br>Good correlation between Gram stain, culture, and multiplex PCR for Gram classification |
| Joseph et al. [23] | 64 patients<br>Acute and delayed-onset post-cataract endophthalmitis<br>64 samples (V only)<br>50 negative controls (50 V) | DNA extraction: QIAamp DNA mini kit (Qiagen)<br>*Quantitative real-time PCR with TaqMan probe and sequencing 16S rDNA primers* | Culture +: 34 % (19/64)<br>16S rDNA PCR +: 66 % (37/64) (number of copies detected ranging from $1.42 \times 10^5$ to $3.64 \times 10^7$ copies/ml)<br>Correlation with culture: 100 % for positive results<br>Samples from control cases were negative |
| Aarthi et al. [28] | 35 patients<br>35 samples (19 V, 16 A)<br>26 postoperative (24 acute, 2 chronic), 5 post-trauma, 3 endogenous, 1 panophthalmitis endophthalmitis | DNA extraction using Qiagen DNA mini kit<br>Reverse transcriptase PCR targeting the 16S rRNA region of eubacterial genome<br>dHPLC-based DNA sequencing | Presence of 2 bacterial genomes in 22 (63 %) specimens<br>RT-PCR + 82.8 %: A (68.7 %) and V (94.7 %) |
| Cornut et al. [39] | 17 eyes with post-traumatic endophthalmitis, 19 samples (12 A, 9 V) | DNA extraction with Qiagen kit (Qiagen)<br>*PCR sequencing 16S rDNA primers* | Culture +: 10 % A, 43 % V<br>PCR positive in 22 % A, 50 % V<br>The PCR performed in 16 patients (94 %) was positive in 62 % of the cases and was necessary for 5 who had negative cultures (29 %)<br>Bacterial identification was obtained in 77 % of the cases |

| | | | |
|---|---|---|---|
| Sugita et al. [26] | 26 bacterial endophthalmitis<br>9 fungal endophthalmitis | DNA extraction using a DNA mini kit (Qiagen)<br>*Broad-range PCR* using the AmpliTaq Gold<br>Real-time PCR 7300 system or the LightCycler 480 II instrument<br>*Primers for 16S rDNA, fungal 18S, or 28S rDNA* | 16S PCR positive in 64 % of bacterial endophthalmitis cases<br>18S/28S fungal PCR positive in 61 % of cases |
| Bharathi et al. [40] | 66 endophthalmitis:<br>66 V in<br>Postoperative (33), post-traumatic (18), endogenous (3) endophthalmitis | DNA extraction using a QIAamp DNA mini kit (Qiagen)<br>*Uniplex, nested, semi-nested, multiplex, and nested multiplex PCRs*<br>Primers for 16S rDNA, *P. acnes*, fungal 18S, or 28S rDNA | V: cultures + (24 %), PCR+ (65 %)<br>15 % *P. acnes* genome<br>Nested PCRs (sensitivity 64 %) are greater than uniplex (56 %) and multiplex PCR (55 %). The increase in sensitivity may be attributed to the two amplification cycles<br>100 % similarities between culture and PCR results<br>53 % of the 50 culture-negative specimens showed positive amplification<br>PCR is sufficient for the diagnosis of 54 % of culture-negative cases |
| Brillat-Zaratzian et al. [9] | 23 eyes with bleb-related endophthalmitis | DNA extraction with Qiagen kit (Qiagen)<br>*PCR sequencing*<br>*16S rDNA primers* | 13 patients had A sampled (culture positive in 45 %, pan-bacterial PCR positive in 70 %, bacterial identification in 70 %)<br>10 patients had V sampled (culture positive in 40 %, pan-bacterial PCR positive in 46 %, bacterial identification in 61 %)<br>By combining results of culture and pan-bacterial PCR, a bacterial species was identified in 73.9 %<br>PCR identified causative microorganism in three-quarters of cases, i.e., 21 % more cases than through culture alone |

*A* aqueous, *V* vitreous, *PCR* polymerase chain reaction, *PPV* pars plana vitrectomy, *RFLP* restriction fragment length polymorphism

Recently, a *reverse transcriptase PCR* [28] was evaluated in 35 endophthalmitis cases with PCR positivity in 38 % of the aqueous samples and 95 % of the vitreous samples. Selecting 16S rRNA as a target gene had several advantages: the 16S rRNA is essential for the viability of all bacteria and is a multicopy gene with a longer half-life as compared to mRNA.

**Multiplex PCR** requires only 2–3 h and can screen rapidly for the presence of a large number of infectious antigens [20, 26]. This real-time PCR may also be used to measure the DNA load. Acute endophthalmitis is usually associated with a high number of bacterial DNA copies [26].

**Specific PCR Techniques** are rarely used as a first-line diagnostic test in endophthalmitis patients [20, 23, 24, 26]. As compared to pan-bacterial PCR, specific PCR tests allow faster (1–3 h) and more sensitive detection of target bacterial species. Goldschmidt et al. [20] reported the use of PCR tests targeting bacterial species belonging to the same bacterial family or genus (*Enterobacteriaceae*, *Propionibacteriaceae*, *Staphylococcus*, *Streptococcus*, *Haemophilus*, *Pseudomonas*, *Acinetobacter*, *Corynebacterium*). Bispo et al. [24] published a series of 14 patients using real-time PCR incorporating marked nucleotides followed by sequencing, also with a 95 % identification rate versus 47.6 % in culture. However, the sequencing could not be interpreted in an appreciable number of cases in this series. Joseph et al. [23] reported a large series of 64 patients, demonstrating the quantitative value of a real-time PCR method, but with lower identification rates: 66 % in PCR and 34 % in culture. These real-time techniques appear to be more sensitive and more rapid than conventional techniques (the amplification and detection procedures are carried out simultaneously in the same tube).

The development of DNA chips, also called DNA microarrays or biochips, i.e., collecting many specific hybridization probes on the same medium, is currently being studied. *DNA microarray technology* allows simultaneous identification of a wide variety of genes, rapid determination of the genetic profile of a microorganism, and parallel identification of different microorganisms in a single assay. This technique has recently been applied to the vitreous specimens of patients infected with *Klebsiella pneumoniae*, *Streptococcus agalactiae*, and *Candida parapsilosis* [29, 42].

**Quantitative Real-Time PCR** The ability to collect quantitative information on bacterial infections in the eye should be useful in helping determine clinical diagnoses and therapeutic follow-ups [11, 26, 27].

### *4.1.4 Contribution of PCR to the Diagnosis of Post-traumatic Endophthalmitis*

Endophthalmitis occurs at a higher frequency following eye trauma than after eye surgery, and post-traumatic endophthalmitis occurs in approximately 7 % of patients

with penetrating eye injuries [43]. *Staphylococcus epidermidis* has been implicated in 22–42 % of these cases, followed by *Bacillus* (11–29 %), *Streptococcus* (11–14 %), and gram-negative bacteria (10–22 %) [43–46]. Gram-negative bacteria are more commonly associated with post-traumatic endophthalmitis cases with an intraocular foreign body.

Mixed infections are significantly more frequent in this context (11–30 %) [45]. The use of denaturing high performance liquid chromatography-based identification of the bacterial genome may be useful since the presence of mixed genomes can be identified separately and easily [28].

Fungal infections account for 5–15 % of cases of post-traumatic endophthalmitis, particularly cases of wound contamination by plant material [47]. In this context, it can be useful to use broad-range real-time PCR for fungi, measuring the amplification of the target fungal 28S rRNA gene or the *Candida* or *Aspergillus* 18S rRNA genes [8, 22]. This latter study [8] showed PCR-positive samples all had significantly high numbers of copies of *Candida*, *Aspergillus*, or *Cryptococcus* DNA.

In a recent series [41], we showed that the pan-bacterial PCR was positive in 62 % of cases and was indispensable to the microbiological diagnosis for five patients who had negative cultures (29 %). Finally, bacterial identification was obtained in 77 % of cases, most of the time gram-positive bacteria. Pan-bacterial PCR is also useful to test for *P. acnes*, which was detected in up to 17 % of patients in one series [43].

### *4.1.5 Contribution of PCR to the Diagnosis of Fungal Endophthalmitis*

The overall incidence of fungal endophthalmitis is low (3–8 % of endophthalmitis cases). The incidence is 13–20 %, however, in areas with tropical climates, such as in Southern Florida [44, 48] and India [45, 49]. Universal primers complementary to a conserved sequence of either the 18S rRNA gene [10, 50] or the 28S rRNA gene [51] common to all fungi have been used with intraocular specimens. Sensitivity has been found higher in vitreous samples than in aqueous humor samples [51].

Other molecular techniques for fungal identification have been reported such as the use of specific nested PCR [52] or semi-nested PCR targeting the internal transcribed spacer region, a multicopy gene (used in molecular taxonomy to determine the species level) [53–55].

More recently, broad-range (18S rRNA sequences) quantitative real-time PCR has been developed and evaluated in patients with endogenous or post-traumatic endophthalmitis ($n=7$) [22]. This technique allowed rapid identification of fungal DNA and quantification of fungal copies for *Candida* and *Aspergillus* DNA.

All these studies suggest that PCR is a more sensitive and rapid diagnostic tool compared with conventional cultures. However, these studies included a limited number of patients, and the sensitivity of PCR techniques should be further analyzed.

## 4.2 Conclusion

To optimize the detection of microorganisms causing endophthalmitis, it is preferable to obtain an early collection of vitreous and to apply both conventional culture and molecular biology techniques (pan-bacterial PCR or real-time PCR), since the two approaches are complementary. For samples collected at the time of vitrectomy, pan-bacterial PCR performed on diluted vitreous is as useful as on undiluted vitreous. PCR-based techniques are more sensitive than culture for the detection and identification of fastidious bacteria (e.g., *Granulicatella*, *Moraxella*, *P. acnes*, and *Mycobacterium* species) and when patients have received an intravitreal antibiotic before the collection of intraocular samples. Recent molecular techniques allow rapid and specific microbiological diagnosis, can screen rapidly for the presence of a large number of infectious antigens, and quantify bacterial loads.

**Conflict of Interest** The authors declare that they have no conflict of interest.

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# Chapter 5
# Acute-Onset Postoperative Endophthalmitis

**Kamyar Vaziri, Nidhi Relhan, Stephen G. Schwartz, and Harry W. Flynn Jr.**

## 5.1 Introduction

Infectious endophthalmitis is an uncommon but potentially severe disease characterized by marked inflammation of intraocular tissues and fluids. Endophthalmitis can be broadly divided into postoperative (acute and delayed onset), post-traumatic, post-intravitreal injection, and endogenous categories [1]. Postoperative endophthalmitis is the most common category, accounting for up to 80 % of all endophthalmitis cases [2]. Acute-onset postoperative endophthalmitis is generally defined as occurring within 6 weeks of surgery, and cataract surgery is responsible for the majority of these cases (Fig. 5.1a, b) [3, 4].

## 5.2 Epidemiology and Clinical Characteristics

### *5.2.1 Incidence*

Reported incidence rates of acute-onset postoperative endophthalmitis following cataract surgery range from 0.03 to 0.2 % [5–13]. Acute-onset postoperative endophthalmitis may also occur following pars plana vitrectomy (PPV) [14–20] (Fig. 5.2), penetrating keratoplasty [5, 21, 22], scleral buckling [23], trabeculectomy

K. Vaziri, MD • N. Relhan, MD • S.G. Schwartz, MD, MBA (✉) • H.W. Flynn Jr., MD
Department of Ophthalmology, University of Miami Miller School of Medicine,
Bascom Palmer Eye Institute, Miami, FL, USA
e-mail: hflynn@med.miami.edu



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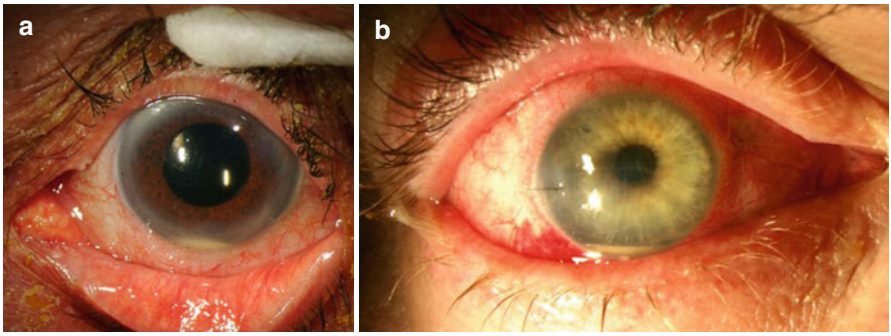


**Fig. 5.1** (**a**) A 60-year-old male presented 9 days after cataract surgery with acute-onset endophthalmitis (*Staphylococcus epidermidis*). Clinical presentation included sudden onset decrease in visual acuity, conjunctival hyperemia, corneal edema, and hypopyon. (**b**) A 69-year-old male with acute-onset endophthalmitis (coagulase-negative staphylococci) presented 3 days after cataract surgery. A suture was placed in temporal clear corneal incision to ensure wound stability after the cataract surgery. However despite that, endophthalmitis occurred

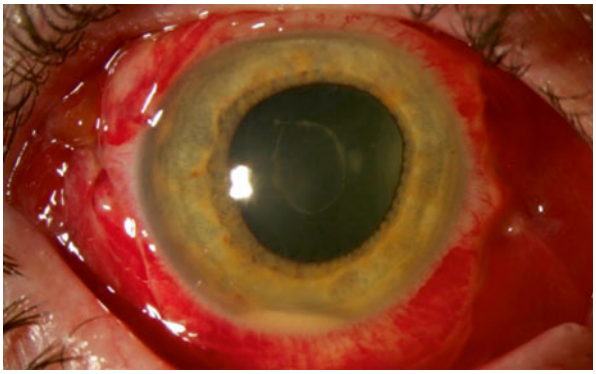

**Fig. 5.2** A 60-year-old patient presented with acute-onset endophthalmitis *(Staphylococcus epidermidis)* 2 days after pars plana vitrectomy (PPV) surgery

[24, 25], glaucoma drainage device implantation [26], and other procedures. Endophthalmitis after trabeculectomy (bleb-related endophthalmitis) is discussed in Chap. 8, and endophthalmitis after scleral buckle or glaucoma drainage device implantation is discussed in Chap. 12.

### *5.2.2 Presentation*

The Endophthalmitis Vitrectomy Study (EVS) was a randomized clinical trial of 420 patients with acute-onset postoperative endophthalmitis following cataract extraction or secondary intraocular lens (IOL) implantation. In the EVS, 94 % of participants presented with decreased visual acuity, 82 % with conjunctival

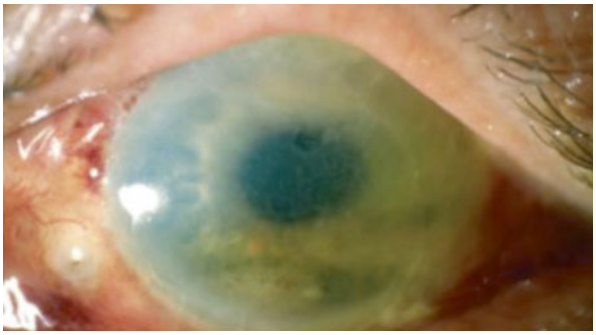

**Fig. 5.3** A 65-year-old female presented post-cataract surgery with toxic anterior segment syndrome. Conjunctival hyperemia and limbus-to-limbus corneal edema are significant

injection, 74 % with eye pain, and 35 % with eyelid edema. Two studies of endophthalmitis after PPV reported similar signs and symptoms, with decreased visual acuity (85–100 % of patients), eye pain (69–78 %), hypopyon (54–78 %), and lid edema (26 %) commonly seen [18, 27]. Most (75 %) cases of endophthalmitis after cataract surgery present within the first week postoperatively.

### *5.2.3 Differential Diagnosis*

The differential diagnosis of acute postoperative endophthalmitis includes toxic anterior segment syndrome (TASS) (Fig. 5.3), exacerbation of pre-existing noninfectious uveitis, retained lens material, and vitreous hemorrhage [28, 29].

TASS is an acute noninfectious inflammatory reaction with uncertain incidence rates, typically occurring within 12–48 h of cataract surgery [30]. TASS is caused by the introduction of toxic substances in the anterior segment of the eye during cataract surgery. The sources of these substances can include irrigating solutions, surgical instruments, perioperative medications, and intraocular lenses [30–32]. Several characteristics may assist in distinguishing TASS from acute-onset postoperative endophthalmitis. In TASS, the inflammation is localized to the anterior chamber without vitreous involvement, and pain is often minimal or absent. Furthermore, TASS typically occurs earlier, usually presenting within the first postoperative day, although delayed-onset cases have also been reported. TASS may occur in clustered outbreaks from a single surgical center [28, 33, 34].

### *5.2.4 Risk Factors*

For cataract surgery, preoperative risk factors for acute-onset postoperative endophthalmitis include blepharitis, diabetes mellitus, and advanced age [12, 35–40]. Intraoperative risk factors include posterior capsular rupture, vitreous loss, and

less experienced surgeons [11, 35, 36, 38–46]. Some series have reported clear corneal incisions and nonuse of intracameral antibiotics as risk factors, but these findings are controversial. Other risk factors include immunocompromised status, IOL type (silicone vs. others), and postoperative wound leak [6, 47, 48].

Immediate sequential bilateral cataract surgery is increasing in popularity, but the risk of bilateral simultaneous acute-onset postoperative endophthalmitis is of concern. In a 2012 survey of the American Society of Cataract and Refractive Surgery (ASCRS) members, only 0.9 % responded that they performed bilateral or same-day cataract surgeries [49]. However, a number of prospective and retrospective studies have reported no cases of bilateral endophthalmitis following this technique [50–52].

For acute-onset endophthalmitis occurring post-penetrating keratoplasty, risk factors include certain surgical indications (including microbial keratitis, trauma, or impending or actual corneal perforation) and infection as the cause of donor death [53]. For acute-onset endophthalmitis occurring after PPV, risk factors include postoperative hypotony and vitreous incarceration in a sclerotomy [20]. At one time it was thought that small-gauge transconjunctival PPV was associated with higher rates of endophthalmitis than was 20-gauge transscleral PPV, but recent series have generally reported similar incidence rates [20].

### *5.2.5 Causative Organisms*

In the EVS, among culture-positive cases (70 % of cases), 94.2 % of isolates were gram-positive bacteria [54]. Among these, coagulase-negative staphylococci (CNS) were the most commonly identified pathogens (70 % of culture-positive cases) followed by *Staphylococcus aureus* (9.9 %) and *Streptococcus* species (9 %) [54]. Coagulase-negative staphylococci are also the predominant isolates reported in endophthalmitis following PPV [17, 18].

In the EVS, cases of fungal endophthalmitis were excluded, as this study was limited to presumed bacterial postoperative endophthalmitis following cataract surgery. Likewise, there are limited reports of fungal postoperative endophthalmitis following cataract surgery in the United States [5, 55]. However, two publications from India reported that fungi caused 17 and 18 % of postoperative endophthalmitis cases, although the type of eye surgery was not specified; the 18 % figure is for cases occurring within 30 days postoperatively [56, 57]. A study from India of over 15,000 cataract surgeries reported 10 cases of culture-positive endophthalmitis; 1 (10 %) was fungal [58].

Clustered outbreaks of acute-onset postoperative endophthalmitis following cataract surgery may be associated with relatively specific causative pathogens. Such outbreaks are typically caused by specific sources of contamination and the microbial profile typically associated with those sources. In a systematic review of 27 studies reporting outbreaks of acute-onset postoperative endophthalmitis, it was reported that gram-negative bacteria were the most common causative organisms

(65.2 %) followed by gram-positive bacteria (21.7 %) and fungi (14.8 %). The most common potential source of contamination was the intraoperative irrigating fluid (37 %) [59].

## 5.3 Diagnosis

### *5.3.1 Background*

Endophthalmitis is a clinical diagnosis, subsequently confirmed with laboratory testing of vitreous or aqueous. Typically, empiric broad-spectrum antibiotics are used, but identifying the causative microorganisms becomes important in assessing antibiotic susceptibility and also in guiding treatment in cases that do not respond to initial therapy.

Vitreous cultures generally provide more accurate and reliable culture results than do aqueous cultures [60–63]. In one series, 48 % of the cases with negative aqueous cultures had positive vitreous cultures [64]. Vitreous specimens may be obtained by vitreous tap using a needle and syringe, PPV, or office-based automated vitrectors [65, 66]. No significant differences were reported in the positivity of cultures obtained from vitreous tap/biopsy versus PPV in the EVS [63].

### *5.3.2 Challenges in Diagnosing Specific Classes of Endophthalmitis*

Most series of acute-onset postoperative endophthalmitis cases reported culture-positive rates of over 70 % [5, 11, 64], but some series have reported rates below 60 % [67, 68].

### *5.3.3 Recent Advances in Identifying Pathogens*

There is interest in the rapid and accurate detection of microorganisms beyond the use of traditional culture media [69]. Real-time polymerase chain reaction (PCR) has been reported to identify both bacteria [70, 71] and fungi [72, 73]. In one series, the rate of detection of bacteria in aqueous and vitreous samples increased from approximately 48 % to over 95 % using PCR [71]. In a prospective study from India of 64 eyes presenting with presumed bacterial endophthalmitis up to 1 year following cataract surgery (mean 25 days), quantitative real-time PCR detected the presence of 16s rDNA consistent with bacteria in 66 % of vitreous samples, while conventional culture was positive in only 34 % [74]. The authors note that it is possible that cases that were negative by both culture and PCR were not due to infection. Other

**Fig. 5.4** Outpatient procedure of vitreous "tap" (aspirate), performed using a butterfly needle attached to a 10-cc syringe, to obtain the intraocular fluid sample for microbiological evaluation. The sample may also be obtained using a short 23- or 25-gauge needle attached to a 3-cc syringe

techniques include matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry [75, 76] and magneto-DNA nanoparticle systems; the latter technique was reported to identify 13 species of bacteria in under 2 h [77]. The microbiological and molecular methods for diagnosing endophthalmitis are discussed in Chaps. 3 and 4.

## 5.4 Treatment

The EVS randomized patients with acute postoperative endophthalmitis to receive either PPV or vitreous "tap/biopsy." The "tap/biopsy" category allowed sampling of the vitreous by either needle aspirate or biopsy using a vitrector. The EVS reported that in patients with initial visual acuity of light perception (LP), when compared to tap/biopsy and inject (Fig. 5.4), prompt (within 6 h) PPV was associated with a threefold increase in the proportion of patients achieving visual acuity of at least 20/40, a twofold increase in the proportion of patients achieving visual acuity of at least 20/100, and a decrease in the proportion of patients achieving visual acuity of worse than 5/200. In patients with initial visual acuity of better than LP, tap/biopsy and inject had comparable outcomes to PPV (Fig. 5.5) [54]. Based on these results, PPV is generally recommended in patients with post-cataract endophthalmitis presenting with initial visual acuity of LP, and tap and inject is generally recommended for eyes presenting with better initial visual acuities (Table 5.1).

In some clinical settings, it may not be practical to perform PPV in the early period, even in eyes in which immediate PPV would be recommended. In these circumstances, a reasonable option is to treat with tap and inject and then perform PPV as soon as surgery can be arranged. The initial injection of empiric vancomycin plus ceftazidime may not sterilize the vitreous, as illustrated in a case report in which cultures obtained at PPV were still positive 4 h after the initial injection of antibiotics although the bacterial isolate was susceptible [78]. Because of the possibility of delayed sterilization, a repeat injection of vancomycin plus ceftazidime

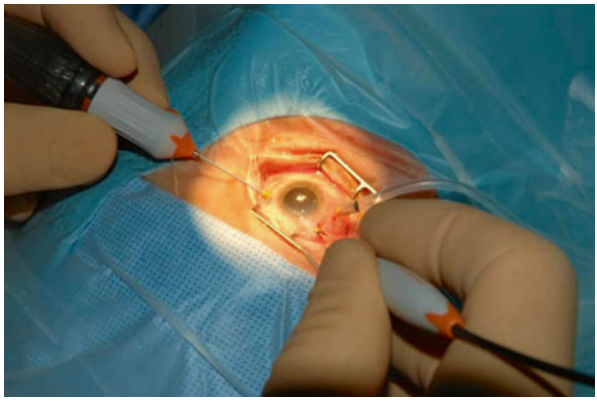

**Fig. 5.5** Standard 23-gauge pars plana vitrectomy (PPV) performed for endophthalmitis

**Table 5.1** Medication regimens for acute-onset postoperative endophthalmitis following cataract surgery

| Treatment | EVS treatment regimen | Authors' recommended regimen |
|---|---|---|
| Intravitreal antibiotics | Vancomycin 1 mg/0.1 ml and amikacin 0.4 mg/0.1 ml | Vancomycin 1 mg/0.1 ml and ceftazidime 2.25 mg/0.1 ml (ceftriaxone 2 mg/0.1 ml may be used instead of ceftazidime) |
| Intravitreal steroids | None | Dexamethasone 0.4 mg/0.1 ml (optional) |
| Subconjunctival antibiotics | Vancomycin 25 mg and ceftazidime 100 mg | Vancomycin 25 mg and ceftazidime 100 mg (optional) |
| Subconjunctival steroids | Dexamethasone 6 mg/0.25 ml | Dexamethasone 12–24 mg (optional) |
| Topical antibiotics | Vancomycin 50 mg/ml and amikacin 20 mg/ml | Vancomycin 25 mg/ml and ceftazidime 50 mg/ml or commercially available topical antibiotics (optional) |
| Topical steroids and cycloplegics | Prednisolone acetate drops and 1 % atropine or 0.25 % scopolamine | Prednisolone acetate and a cycloplegic agent (optional) |
| Systemic antibiotics | Ceftazidime 2 g q8h and amikacin 7.5 mg/kg initial dose followed by 6 mg/kg q12h (vs. none) | Usually none. May consider oral fluoroquinolones in selected cases |
| Systemic steroids | Prednisone 30 mg twice a day for 5–10 days | None |

is usually given at the end of the PPV even if patients received these antibiotics with an earlier tap and inject.

In a more recent retrospective study, 21 eyes with acute-onset postoperative endophthalmitis were treated with initial PPV. Following PPV, endophthalmitis resolved in 100 % of patients with close to 67 % of patients achieving visual acuity of 20/400, while only 9.5 % of eyes had this vision prior to PPV [79].

The use of systemic antibiotics in the treatment of acute-onset postoperative endophthalmitis is controversial. The EVS reported that systemic amikacin and ceftazidime had no significant effect on outcomes in postoperative endophthalmitis [54]. These systemic antibiotics have little efficacy against staphylococci, the etiology of approximately 80 % of culture-positive EVS cases, and systemic amikacin penetrates into the vitreous very poorly. Fourth-generation fluoroquinolones, which were not tested by the EVS, achieve therapeutic levels from the systemic circulation even in noninflamed eyes [80], but their benefits in endophthalmitis remain unproven. One study compared the use of oral ciprofloxacin versus moxifloxacin in patients with acute-onset postoperative endophthalmitis following cataract surgery and reported that the group treated with oral moxifloxacin had a faster resolution of hypopyon and a decreased need for repeat intravitreal antibiotics [81].

A literature review of studies evaluating the adjunct role of intravitreal corticosteroids with intravitreal antibiotics in acute endophthalmitis reported no definite benefit to their use [82].

In a series of 59 patients with endophthalmitis following cataract extraction, glaucoma filtration procedures and trauma, and treated with tap and inject, the addition of subconjunctival antibiotics did not have a significant impact on final visual acuities [83].

Antibiotic resistance is an important potential concern [84]. The EVS study investigators reported that 99.4 % of bacterial isolates were susceptible to either vancomycin or amikacin [85]. Gram-positive bacteria, particularly coagulase-negative staphylococci, are the predominant causative pathogens in acute-onset postoperative endophthalmitis. In a single-center study of 327 endophthalmitis cases from 2002 to 2011, 100 % of gram-positive causative bacteria were susceptible to vancomycin, and 100 % of gram-negative bacteria were susceptible to ceftazidime [86]. In another series of coagulase-negative staphylococci isolated from 68 patients with acute-onset postoperative endophthalmitis, 100 % of isolates were susceptible to vancomycin, but only 70 % were susceptible to fluoroquinolones [87].

### *5.4.1 Complications of PPV for Treatment of Acute-Onset Endophthalmitis*

PPV is associated with a number of complications [88, 89]. In the EVS, complication rates from PPV were relatively low with a total of 2/218 (0.72 %) with microhyphema, 5/218 (2.3 %) with wound leak, 2/218 (0.72 %) with dislocated IOL, and 1/218 with (0.46 %) with choroidal detachment [54]. The EVS investigators reported no significant differences in the rates of post-treatment retinal detachment in eyes treated with PPV versus tap and inject (7.8 % vs. 9.0 %) [90]. In a more recent series of 70 eyes undergoing PPV for acute-onset postoperative endophthalmitis, the most common complications following PPV were retinal detachment (13.3 %), corneal edema (10.3 %), and retinal tear (8.6 %) [91].

## 5.5 Visual Outcomes

### *5.5.1 Acute-Onset Postoperative Endophthalmitis*

In the EVS, only 53 % of treated eyes had a final visual acuity of 20/40 or better, and 15 % had a final visual acuity of 20/200 or worse [54]. Similarly, in a more recent single-center series, 50 % of eyes with acute-onset postoperative endophthalmitis had a final visual acuity of 20/40 or better, and overall more than 36 % had a final visual acuity of worse than 20/200 [5]. An important predictor of final visual outcome is the infecting organism. A large retrospective series reported that eyes with final visual acuity of 20/40 or better were more likely to be culture-negative or culture-positive for coagulase-negative staphylococci [11]. In another series, endophthalmitis due to coagulase-negative staphylococci was associated with a favorable final visual outcome (20/40 or better), while streptococcal endophthalmitis was associated with an unfavorable (worse than 20/200) outcome [92]. A study of 615 post-cataract endophthalmitis cases in a Medicare population in the United States reported that cases due to streptococci were 10 times more likely to have poor final visual acuity than those due to coagulase-negative staphylococci [93].

## 5.6 Prophylaxis

### *5.6.1 Postoperative Endophthalmitis*

Endophthalmitis cannot be completely prevented, but its incidence can be significantly reduced with the use of preoperative povidone-iodine antisepsis [94, 95]. A prospective randomized trial of 131 eyes undergoing intravitreal injections showed that with at least 30 s of exposure to 5 % povidone-iodine, colony-forming units of conjunctival bacteria decreased significantly (Fig. 5.6a, b) [96]. The European Society of Cataract Surgery (ESCRS) performed a randomized controlled trial and reported that intracameral cefuroxime during phacoemulsification reduced the incidence of postoperative endophthalmitis by approximately fivefold [38]. These results were replicated in later studies originating from multiple countries [97–102], along with a systematic review and meta-analysis of the ESCRS and 17 observational studies [103]. A Canadian case control study of 75,318 eyes undergoing cataract surgery, however, did not find a significant benefit to the use of intracameral antibiotics in reducing postoperative endophthalmitis rates [104].

Despite the results, the use of intracameral antibiotics remains controversial [105] although they appear to be more commonly used in Europe. In 2012, ASCRS reported that only 22.8 % of its members used intracameral antibiotics [49]. However, a survey of 250 European surgeons reported that 74 % of respondents used intracameral antibiotics and over 90 % of respondents would have used cefuroxime if it were commercially available in a single-unit dose [106].

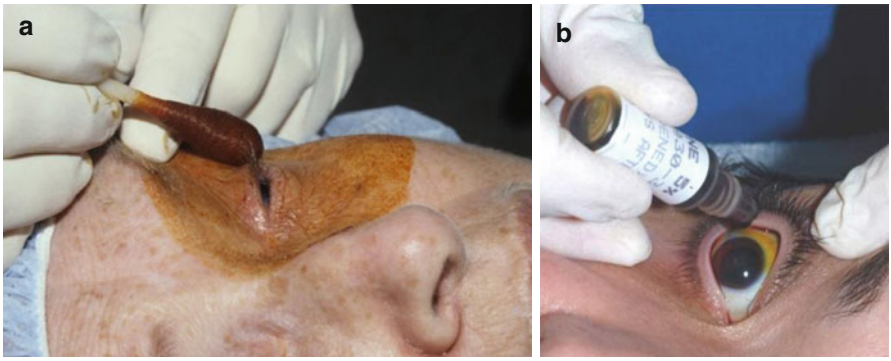


**Fig. 5.6** (**a**) Preoperative full preparation of lids and lashes with 10 % povidone-iodine. (**b**) Preoperative conjunctival preparation with 5 % povidone-iodine

The prophylactic efficacy of topical antibiotics in postoperative endophthalmitis is also controversial. A 2007 survey from the ASCRS reported that 88 % of respondents used preoperative, 91 % used perioperative, and 98 % used postoperative topical antibiotics [107], but no randomized controlled trials have been published regarding their efficacy. Preoperative topical antibiotics significantly reduce conjunctival flora [108, 109], but it is uncertain if this actually decreases endophthalmitis rates. In the ESCRS study, patients who received perioperative topical levofloxacin did not have significantly different postoperative endophthalmitis rates following cataract surgery compared with patients who did not receive such treatment [38]. One series reported that substituting a combination of postoperative topical antibiotics and corticosteroids with topical corticosteroids alone did not significantly change the incidence of endophthalmitis [110]. Similarly, a systematic review did not find a beneficial role of topical antibiotics in reducing the rates of post-cataract surgery endophthalmitis [103].

The prophylactic use of subconjunctival antibiotics to protect against acute-onset postoperative endophthalmitis is also controversial, but a number of studies do support this technique. A series of 13,886 consecutive cataract surgeries reported that subconjunctival antibiotics were associated with a significantly reduced rate of acute-onset postoperative endophthalmitis [111]. In another series, it was reported that subconjunctival antibiotics were associated with a significantly lower risk of developing postoperative endophthalmitis [112].

The addition of antibiotics to the irrigation solution is also controversial. Certainly endophthalmitis may develop despite prophylactic irrigation with antibiotic solutions. The EVS in 1996 reported that 11.5 % (10/87) of the endophthalmitis patients included in the study and for whom such data were recorded had received prophylactic antibiotics in the cataract infusion fluid during initial cataract surgery [85]. In 2012, the ASCRS reported that only 21.7 % of responding members used this approach [49]. A series of 644 eyes that underwent cataract surgery compared 322 "control" eyes given balanced salt solution irrigation with 322 eyes given irrigation with antibiotic (vancomycin plus gentamicin) solution and found that only the control group had any cases of postoperative endophthalmitis (two cases) [113].

However, the rate of endophthalmitis was not statistically different between the groups [114], and these two endophthalmitis cases occurred in surgeries complicated by posterior capsular rupture, a known risk factor for endophthalmitis. In a recent retrospective series from Spain of 18,287 cataract surgeries over a 13-year period, it was reported that after switching from gentamicin subconjunctival injection to the addition of gentamicin and vancomycin to the irrigation fluid, the rate of postoperative endophthalmitis decreased [115]. Use of gentamicin or other aminoglycosides in the infusion fluid may carry a risk of retinal toxicity, however, especially if dosing errors occur during compounding. In addition, a number of cases of macular infarction have occurred following subconjunctival injection of aminoglycosides given for prophylaxis after eye surgery [116, 117]. Recently, cases of hemorrhagic occlusive retinal vasculitis (HORV) have been reported in patients after cataract surgery where intracameral vancomycin was injected [118].

Similarly, the use of prophylactic oral antibiotics is controversial in this setting. In a recent prospective study of 42 patients receiving either oral or topical moxifloxacin prior to cataract surgery, it was reported that in both groups, the aqueous concentration of this antibiotic was well above the $MIC_{90}$ (minimum inhibitory concentration needed to inhibit the growth of 90 % of bacteria) levels required to eliminate the majority of endophthalmitis-causing pathogens [119]. The study did not address efficacy of oral antibiotic prophylaxis in preventing postoperative endophthalmitis.

A retrospective cohort study of 25,410 surgeries reported that postoperative endophthalmitis rates were significantly lower when an injectable IOL was used when compared with forceps-inserted foldable IOLs [120].

## 5.7 Conclusion

Acute-onset postoperative endophthalmitis is an uncommon but serious complication. The EVS provided valuable guidelines for the management of this disease that are still beneficial today. Treatment outcomes may be poor, even with prompt and appropriate therapy. Therefore, risk reduction remains very important. Topical preoperative povidone-iodine is well established as an important step. Even though intracameral antibiotics are widely used, particularly in Europe, the efficacy of this approach remains controversial.

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# Chapter 6
# Chronic Endophthalmitis Masquerading as Uveitis

**Rachael Niederer, Asaf Bar, Rosie Gilbert, Lazha Talat, Efthymia Pavlidou, Malgorzata Woronkowicz, Sophie Seguin-Greenstein, Sue Lightman, and Oren Tomkins-Netzer**

Uveitis is a term synonymous with intraocular inflammation which can be defined by the parts of the eye it affects (anterior, intermediate, posterior, and panuveitis) or by tempo as acute, generally lasting 3 months or less, or chronic lasting more than 3 months [1]. It has a variety of etiologies which can be broadly divided into immune mediated, infectious, and masquerade types. Immune mediated may occur with a systemic disease such as ankylosing spondylitis, Behcet's disease, or multiple sclerosis or be idiopathic and appear to be confined to the eye. Infectious causes are legion and may occur with a systemic infection such as toxoplasmosis or tuberculosis or as a reactivation of latent viral infection in the eye such as acute retinal necrosis. Other causes may mimic these such as lymphoma or following retinal detachment, and the underlying pathology in these eyes needs to be identified by thorough clinical examination.

Microbial organisms can be introduced into the eye during surgery or following penetrating trauma. When endophthalmitis ensues, the onset is usually acute, with symptoms of eye pain and decreased vision beginning within a few days after surgery or trauma, and with a hypopyon and severe vitritis found on examination. Acute postoperative endophthalmitis is discussed in Chap. 5 and post-traumatic endophthalmitis in Chap. 9. Much less commonly, organisms of low virulence may cause intraocular inflammation often weeks after the surgery or penetrating injury. After cataract surgery, these organisms are typically *Propionibacterium acnes* and coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*) but also fungi. Following penetrating trauma particularly with a foreign body from the environment,

R. Niederer, BHB, MBChB, PhD • A. Bar, MD • R. Gilbert, MBBS, MRCOphth • L. Talat, MPH, MSc (Ophth) • E. Pavlidou, MD, MSc • M. Woronkowicz, MD • S. Seguin-Greenstein, MBBS, BSc • S. Lightman, MBBS, PhD, FRCOphth • O. Tomkins-Netzer, MD, PhD (✉)
Department of Clinical Ophthalmology, University College London, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, UK
e-mail: s.lightman@ucl.ac.uk; o.tomkins-netzer@ucl.ac.uk



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e.g., a thorn or piece of wood, very low-grade organisms may take a while to manifest. In anyone presenting with uveitis, it is important to ask about recent intraocular surgery or injury – if the person did not have uveitis prior to the surgery or injury and only one eye is involved, infection must always be at the top of potential diagnoses.

## 6.1 Epidemiology and Risk Factors

Chronic endophthalmitis is defined as a bacterial or fungal intraocular infection that has an indolent course extending over weeks to months before a correct diagnosis is made; most cases occur postoperatively. There is some controversy over the definition. Some authors use a defined time (e.g., >6 weeks postoperatively) for onset of either symptoms or diagnosis of endophthalmitis in their definition of chronic endophthalmitis [2], while other authors use only the clinical features of chronic endophthalmitis to define the entity, regardless of time of onset postoperatively [3]. Chronic endophthalmitis frequently masquerades as autoimmune uveitis [4]. The organism can reach the eye through penetrating trauma or surgery (exogenous) or rarely hematologic seeding (endogenous) [5]. The development of symptoms is often gradual so the correct diagnosis may be delayed with subsequent erroneous long-term treatment with corticosteroids [6].

The reported incidence of postoperative endophthalmitis ranges from 0.01 to 0.37 %, varying among different surgical procedures and across studies and different countries [7, 8]. Some studies have reported a recent rise in incidence related to the change in surgical technique toward clear corneal sutureless wounds that allow exogenous organisms easier access to the intraocular space [9]. Nearly all cases reported are acute postoperative endophthalmitis, with rapid onset and acute symptoms. The ratio of acute to chronic postoperative endophthalmitis is unknown [3]. In one single-center study from Saudi Arabia, the reported rate of chronic onset endophthalmitis following cataract surgery was 0.017 % [2].

Risk factors for developing acute postoperative endophthalmitis include preoperative risk factors such as diabetes mellitus, blepharoconjunctivitis, and dry eyes and perioperative risk factors, such as use of Prolene loops and wound abnormalities. The risk factors for chronic endophthalmitis have not been identified.

Though endophthalmitis denotes inflammation secondary to bacterial or fungal infection, many potential noninfectious causes of chronic inflammation arise after intraocular surgery. These can include inflammation related to lens malposition causing constant iris trauma that can contribute to chronic inflammation or from contact of the lens optic with the pupillary margin or trauma to the ciliary body by the lens haptics [3]. Retained cortical material can also cause persistent chronic low-grade inflammation, may be present in the capsular bag, or lost in the vitreous after capsular rupture [10]. These compound the diagnosis of chronic endophthalmitis and must be considered in cases of prolonged inflammation following ocular surgery.

## 6.2 Etiology

In clinical practice, suspected endophthalmitis is managed as though it is of infectious etiology, until proven otherwise, due to the potential severe sight-threatening consequences of untreated infection. While acute endophthalmitis is typically related to virulent bacteria or fungi, chronic low-grade infections may occur postoperatively and post-trauma, are related to organisms of low virulence, and may masquerade as noninfectious uveitis.

Chronic postoperative endophthalmitis typically follows cataract surgery with posterior chamber lens implantation. The onset of symptoms occurs several weeks to many months after surgery. In one study, the onset of inflammation occurred 1 week to 12 months postoperatively, but the diagnosis was made 2 weeks to 38 months postoperatively [11]. Chronic postoperative endophthalmitis is characterized by repeated episodes of low-grade anterior chamber inflammation and vitritis, which may respond to topical corticosteroids at least in the early stages. Post-cataract surgery chronic endophthalmitis is usually (in approximately 40–60 % of cases) caused by *P. acnes* [12], a gram-positive anaerobic bacillus. Less frequently, chronic or delayed-onset postoperative endophthalmitis may also be caused by *P. granulosum*, coagulase-negative staphylococci, or fungi [13–15].

Postoperative fungal endophthalmitis is rare in Western countries and more common in tropical climates. When it does occur, it often presents as a chronic, indolent intraocular inflammation. For this reason presentation and diagnosis may be delayed, for example, until at least 1–2 months after surgery. Molds, such as *Fusarium*, caused 16.7 % of 112 culture-positive postoperative and 14 % of 113 culture-positive post-traumatic endophthalmitis cases in a series from India [16, 17].

A less common cause of chronic endophthalmitis is endogenous fungal endophthalmitis. This results from fungemia, most often candidemia, and usually occurs in hospitalized or recently hospitalized patients, often as a complication of an indwelling central venous catheter. While *Candida* endophthalmitis is typically acute, low-grade inflammation can occur, with the appearance of distinct choroidal lesions and mild vitreous inflammation.

## 6.3 Clinical Presentation

Diagnosis of chronic endophthalmitis can be difficult and may frequently be delayed, as the presentation is that of insidious, grumbling inflammation associated with less virulent organisms and can commonly be mistaken for immune-mediated uveitis [18]. It is important to maintain a high index of suspicion in these cases, as initial investigations including aqueous and vitreous sampling may be negative, and the inflammation may appear to respond, initially, to topical corticosteroids. Prompt and accurate diagnosis is essential to ensure the best possible outcome in these

subjects [3]. Red flags that prompt the physician to strongly consider a diagnosis of chronic endophthalmitis include:

- Prolonged inflammation following surgery, trauma, or infectious keratitis, in a subject with no previous history of uveitis
- Inflammation following surgery, trauma, or infectious keratitis, unable to be weaned from topical steroid, or vision deteriorating due to vitritis and/or macular edema
- Posterior capsule plaque
- Appearance of a hypopyon following neodymium-yttrium aluminum garnet (YAG) capsulotomy

As chronic endophthalmitis may present as a low-grade chronic inflammation over 6 weeks following intraocular surgery or penetrating eye injury, close examination is required in any subject with a history of trauma, as it is possible that the injury was not initially recognized as penetrating at the time of presentation. Endophthalmitis may also complicate infectious keratitis, in approximately 0.5 % of cases, especially in subjects with fungal keratitis, chronic topical steroid use, corneal perforation, or relative immune compromise [19]. Key history that should raise the suspicion of chronic endophthalmitis following intraocular surgery, penetrating trauma, or keratitis is prolonged uveitis in a subject with no previous history of inflammation and either inadequate response to topical corticosteroid or the inability to wean them [3].

Symptoms of chronic endophthalmitis differ from acute endophthalmitis; the subject may report only minor discomfort, and visual acuity may be preserved until late in the presentation. Subjects will often report a history of grumbling inflammation and prolonged topical steroid use following surgery, trauma, or keratitis [19, 20]. Inflammation may wax and wane, but tends to worsen gradually over time. Signs that suggest a diagnosis of chronic endophthalmitis as opposed to uveitis include granulomatous keratic precipitates, hypopyon, whitish nodules at the site of the corneal wound or overlying the intraocular lens (Fig. 6.1), posterior capsule plaque (Fig. 6.2), and vitritis, especially if a “fluff ball” or “string of pearls” is seen in the vitreous [18, 20]. Keratic precipitates are common in both uveitis and chronic endophthalmitis, but are often granulomatous in chronic endophthalmitis, which should prompt the clinician to consider infection if the subject has no other risk factors for granulomatous inflammation (such as sarcoidosis or tuberculosis) [12, 18, 20]. Hypopyon may occur in around half of chronic endophthalmitis cases following surgery or trauma and has been reported in 90 % of cases following infectious keratitis (Fig. 6.3) [18–20]. Beaded fibrin strands may be observed in the anterior chamber in one-third of cases occurring secondary to *P. acnes* [12]. Fungal cases may have an inflammatory mass in the anterior chamber or whitish nodules at the site of corneal wound or scar and are more likely to be associated with corneal edema [3].

Even in the absence of a full clinical picture of endophthalmitis, the presence of a posterior capsule plaque, or whitish nodules over the intraocular lens, should prompt the clinician to strongly consider a diagnosis of chronic endophthalmitis

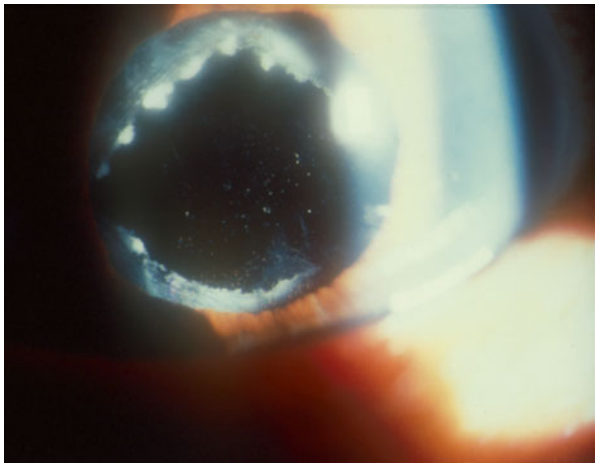

**Fig. 6.1** *Propionibacterium acnes* plaques around the equator of an intraocular lens. Note the granulomatous keratic precipitates on the cornea endothelium

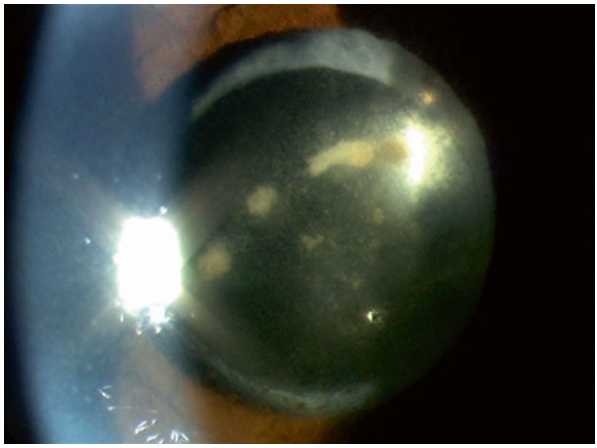

**Fig. 6.2** Colonies of *Propionibacterium acnes* on the posterior capsule behind an intraocular lens

[18, 20–22]. Posterior capsular plaques are not exclusive to *P. acnes* and have also been described with other low-virulence organisms, such as *S. epidermidis*, *Corynebacterium*, or *Mycobacterium* of fungi [3, 23]. The plaques may be located in the peripheral lens capsule, and occasionally a hypopyon may be observed within the capsular bag, prompting maximal dilation when examining these subjects and use of a gonioscopy lens [3, 23].

Some subjects will present with an isolated, white posterior capsular plaque in the absence of any inflammation. Such a presentation has previously been termed "localized endophthalmitis," which occurs when low-virulence organisms are sequestered in the capsular bag following cataract surgery [24]. This

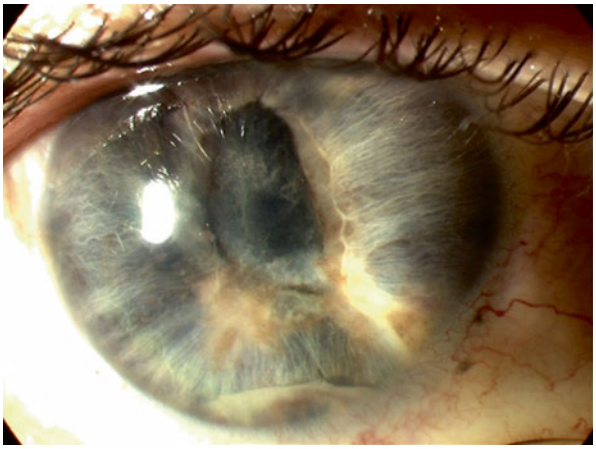

**Fig. 6.3** Anterior uveitis with extensive fibrin and a hypopyon in a patient who developed chronic endophthalmitis from *Alternaria alternata* following a penetrating injury from the thorn of a *Yucca* plant

presentation can mimic posterior capsular opacification. If YAG laser posterior capsulotomy is performed for presumed posterior capsular opacification, the previously sequestered organisms may be released into the vitreous cavity, resulting in generalized endophthalmitis, presenting with an anterior uveitis, hypopyon, and vitritis [24, 25].

Vitritis in chronic endophthalmitis is variable and is more common in late presentations. If fundal view is inadequate, B-scan ultrasonography is essential, to identify vitreous opacities. A vitreous "fluff ball" or "string of pearls" is suggestive of fungal endophthalmitis (Fig. 6.4) [3, 22]. Special vigilance is required in subjects at increased risk of endophthalmitis, such as complicated cataract surgery with posterior capsule breach, trauma involving organic material, diabetes, and immunosuppression.

## 6.4 Diagnosis and Laboratory Investigations

The diagnosis of chronic endophthalmitis should be considered in cases of persistent inflammation in the wake of ocular surgery or penetrating trauma. A detailed history is needed including history of ocular trauma or surgery with a focus on the type of ocular surgery performed and details about the procedure and the presence of any operative complications such as a ruptured lens capsule. Patients will generally complain of mild ocular pain, visual deterioration, and red eye, which gradually develop over several weeks. They typically will report that following the inciting event there was an improvement in symptoms, but with a return of symptoms after several weeks. Examination can reveal conjunctival injection and low-grade granulomatous

**Fig. 6.4** Hazy vitreous with a typical "string of pearls" in a patient with chronic endophthalmitis due to *Candida albicans* following cataract extraction surgery

anterior uveitis, including presence of anterior chamber cells, flare, fibrin formation, capsular thickening, and even a hypopyon [26]. A partial response of early inflammation to topical corticosteroids can also mislead and delay the diagnosis.

Routine vitreous cultures are usually inadequate for the diagnosis as they are positive in less than 50 % of chronic postoperative endophthalmitis cases. The diagnosis of chronic endophthalmitis secondary to *P. acnes* may be delayed due to its slow growth on culture media, with a mean time of 7.9 days (range, 4–14 days) [26] as well as the need for special conditions such as anaerobic cultures or with high $CO_2$ concentrations (Fig. 6.5). Likewise, the diagnosis of chronic endophthalmitis secondary to fungal infections can also be delayed, resulting in adequate treatment initiated up to 2 weeks following the occurrence of symptoms [27]. Samples for culture and sensitivity tests are usually obtained from the anterior chamber aqueous (0.1 ml) and vitreous (0.2 ml). If these cultures are sterile and there remains a strong suspicion of infection, other samples can be taken such as from the posterior capsule or intraocular lens. It is preferred to obtain cultures of both anterior chamber and vitreous taps, especially in cases of endophthalmitis associated with keratitis where positive cultures from aqueous samples have been observed in the presence of negative cultures from a vitreous tap [28]. Furthermore, isolating the organisms may be a challenge as many grow in anaerobic conditions and may only be grown from samples obtained from the lens and capsular bag (Fig. 6.6). Samples should be cultured anaerobically as well as aerobically. Cultures should be plated on both routine (e.g., blood agar, chocolate agar) and fungal (Sabouraud agar) media. A sample also should be placed in broth media (e.g., thioglycollate broth) as this media may grow bacteria when very few organisms are present. Broth will also often grow anaerobic bacteria. In one study of nine cases of

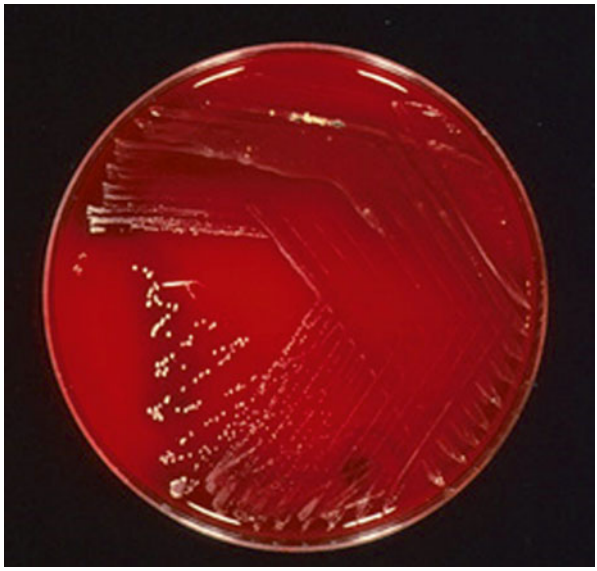

**Fig. 6.5** *Propionibacterium acnes* growing in culture

*P. acnes* endophthalmitis, all nine isolates grew in the thioglycollate broth; six of these also grew on the anaerobic blood agar plate [11]. Monitor the growth of microorganisms for at least 2 weeks [26]. When fungal endophthalmitis is suspected, appropriate staining such as Giemsa and calcofluor white should be performed to observe for the macroscopic and microscopic morphology, such as the shape of the colonies, color, and presence of hyphae.

The introduction of polymerase chain reaction (PCR) testing of vitreous samples obtained from cases of persistent inflammation has resulted in an increased rate of detection of causative organisms, which has led to a tailoring of adequate treatment and a reduction in the use of corticosteroids in infectious cases. In a study of 25 patients with delayed-onset endophthalmitis, aqueous culture and microscopy were diagnostic in 0 % of cases, vitreous culture was positive in 24 %, and PCR from the aqueous and vitreous yielded a positive diagnosis in 84 % and 92 %, respectively [29]. Providing adequate vitreous fluid for both cultures and PCR increases the test yield of identifying potential causative agents. In a study examining the additional information generated by PCR in such cases, identification of *P. acnes* by PCR in cases which were culture-negative did not alter immediate management but prevented subsequent persistence with systemic corticosteroids and earlier recourse to further surgery [30]. Thus, in cases of mild intraocular inflammation managed with a vitreous tap and intravitreal antibiotics with negative culture, a positive PCR result may make the clinician less likely to persist with topical and oral corticosteroids and consider early surgery. Table 6.1 includes a list of pathogens involved in chronic endophthalmitis identified using PCR.

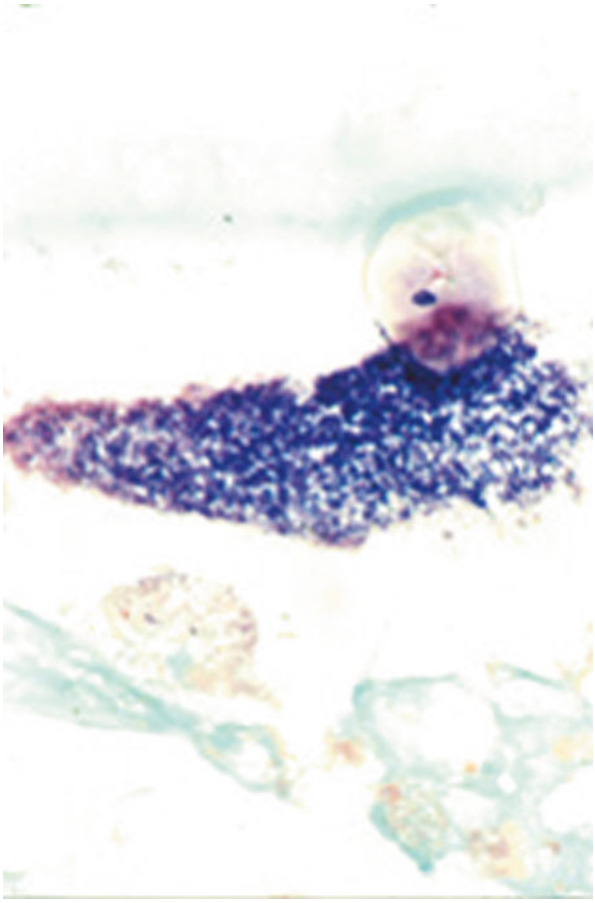

**Fig. 6.6** Histology section stained with hematoxylin-eosin demonstrating *Propionibacterium acnes* inside an extracted capsular bag

**Table 6.1** Chronic endophthalmitis pathogens identified by PCR

| | |
|---|---|
| *Propionibacterium acnes* | Lai et al. [21] |
| *Escherichia fergusonii* | Gokhale et al. [31] |
| *Staphylococcus epidermidis* | Lohmann et al. [29] |
| *Mycobacterium abscessus* | Rolfe et al. [32]; Palani et al. [33] |
| *Mycobacterium fortuitum* | Palani et al. [33] |
| *Enterococcus faecium* | Hernandez-Camarena et al. [34] |
| *Moraxella* spp. | Cornut et al. [35] |
| *Candida albicans* | Jaeger et al. [36] |
| *Fusarium proliferatum* | Ferrer et al. [37] |

## 6.5 Treatment

There is no consensus regarding the treatment strategy of chronic postoperative endophthalmitis. The indolent nature of these organisms, as well as their sequestration within intraocular structure such as the lens capsule, protects them from the host immune response and also from diagnosis. The guidelines set for the treatment of acute postoperative endophthalmitis cannot be extrapolated for these cases, and a treatment protocol is hard to define [3]. The different treatment approaches reported in the literature vary greatly and range between pharmacological treatment alone to several surgical options [2, 18, 26, 38]. Intraocular treatment should be an important component in all approaches [3, 39]. Zambrano et al. reported successful treatment using a nonsurgical approach consisting of intraocular antibiotics with or without topical and subconjunctival antibiotics in three of nine cases of chronic endophthalmitis caused by *P. acnes* [11]. An additional case from that series appeared to respond to topical plus systemic antibiotics alone, with one recurrence retreated this way during 12 months of follow-up. Intraocular antibiotics can either be injected into the capsular bag alone or into the anterior chamber and vitreous cavity simultaneously [40]. As the causative organism is usually unknown at the time treatment must be initiated, broad spectrum antibiotics should be used. When fungal infection is not suspected, empiric intravitreal treatment is with vancomycin (1 mg/0.1 mL), given its broad coverage of the most commonly described causative bacteria, *P. acnes*, and other gram-positive bacteria such as coagulase-negative staphylococci [3]. Other alternative antibiotics such as clindamycin, carbapenems, or chloramphenicol have in vitro activity against *P. acnes*; their use in treating chronic *P. acnes* endophthalmitis has not been established [3, 41]. Kresloff et al. suggested that in cases with very mild inflammation, treatment with antibiotics could be withheld until intraocular cultures, Gram stain, and sensitivity data are obtained. If this approach is considered, patients must be monitored on a daily basis to avoid risk of rapid deterioration and vision loss [5]; depending on the isolated microorganism, the need for further surgical intervention should be assessed. While *S. epidermidis* may respond to intraocular antibiotics, *P. acnes* is commonly resistant to such pharmacological treatment and in many cases requires surgical intervention [42–44].

The addition of surgery to intraocular antibiotics has been suggested by many studies that report that unless the intraocular contents are cleared, the rate of recurrence can be high. Clark et al. found that initial treatment only with an intraocular injection of antibiotics resulted in recurrent or persistent intraocular inflammation in all cases [26]. Even performing a vitrectomy but without a capsulectomy resulted in recurrence in 50 % of their cases, suggesting extensive surgical clearing of the ocular contents including intraocular lens, and lens capsule should be considered when intraocular antibiotics fail to control the infection. Many studies have demonstrated that a cascade approach offers a higher rate or clinical resolution, starting with an intraocular injection of antibiotics and, if there is insufficient response continuing to vitrectomy, removal of the intraocular lens

together with the posterior or entire capsule [11, 26]. Shirodkar and colleagues reported that while recurrent disease occurred in more than 70 % of cases treated with intraocular antibiotics, when PPV with total capsulectomy and IOL exchange or removal were performed, 90 % had complete resolution of endophthalmitis [18].

Due to the rarity of chronic postoperative fungal endophthalmitis, there are only a few case reports describing diverse treatment approaches chosen on a per-patient basis [45–47]. This includes use of intraocular, intravenous, and oral antifungals, corticosteroids, and vitrectomy [3, 45, 47, 48]. The most widely used treatment protocol includes performing a vitrectomy and injecting intravitreal amphotericin (5–10 mg/0.1 mL) or voriconazole, a systemic antifungal drug [6, 49–51], with prolonged systemic treatment for 4 weeks to 6 months [51]. Exogenous fungal endophthalmitis is discussed in detail in Chap. 11.

When considering treatment for chronic endophthalmitis, the causative event may direct the approach physicians take, as well as offer clues to potential causative organisms. Chronic endophthalmitis following surgery is typically related to a single pathogen, with *P. acnes* and coagulase-negative bacteria the most common causes to be considered and treated even before definitive identification is reached. However, in cases of trauma that lead to chronic endophthalmitis, several factors complicate the therapeutic approach, including previous tissue damage, mixed infection from several pathogens, and a higher likelihood of fungal infection. Thus, broader-spectrum antibiotics and earlier tissue debridement may be warranted to avoid a poor visual outcome.

## 6.6 Complications and Visual Outcome

In many cases chronic endophthalmitis is complex to diagnose and to manage, and as such, treatment may be delayed with patients receiving inadequate or no treatment for long periods of time. The visual outcome of these patients is generally poorer than that of patients with acute endophthalmitis, and in most reports over 50 % of cases result in a vision worse than 20/40 [2, 6, 18, 26] with approximately a quarter having a final vision of 20/400 or worse. The mechanism of infection is an important predictor of the final visual acuity, with eyes suffering trauma faring worse than those with postoperative chronic endophthalmitis. This is due to the added damage caused by the trauma itself [52], presence of an intraocular foreign body [53], risk of a polymicrobial infection [54], and retinal detachment that occur in many cases [55]. Furthermore, the virulence of the pathogen and timely initiation of treatment also correspond with the final visual acuity, as they do in acute endophthalmitis [53, 56]; so in general the better the initial visual acuity at the time treatment is initiated, the more favorable the final visual outcome [57]. When vision loss occurs, it is typically related to structural ocular damage, extensive retinal detachment, refractory glaucoma, or chronic cystoid macular edema [26, 52]. Most reports agree that these factors are more important in determining the final visual outcome than the treatment approach [58].

In conclusion, the diagnosis of chronic endophthalmitis is complicated by the presence of nonspecific signs and symptoms, often together with long period of time between the inciting event and the clinical presentation. A high level of suspicion is indicated in cases of uniocular prolonged uveitis, with any history of ocular procedures or trauma, and prompt treatment should be initiated, even before definitive diagnosis of the pathogen is achieved. The most common chronic endophthalmitis pathogens, such as *P. acnes* and fungi, have special culture requirements and may grow very slowly. A reasonable approach is initially based on the severity of the infection and on the causative organism as it is revealed later. In most cases surgical intervention of some sort will be required.

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# Chapter 7
# Endophthalmitis After Intravitreal Injections

**John B. Miller, Luis J. Haddock, and Joan W. Miller**

## 7.1 Introduction

The poor ocular penetration, particularly to the posterior segment, of systemic medications previously limited therapeutic options for treating ophthalmic disease without systemic complications. The use of intravitreal injections has greatly increased the treatments available for previously blinding conditions. Intravitreal injections now represent one of the most common office-based procedures in the United States [1].

The vitreous fills the space between the lens and the retina, presenting a large cavity for the administration of intraocular medications. Unfortunately, this also provides a relatively closed system for the development and proliferation of microbial organisms. Endophthalmitis represents the most feared complication of intravitreal injection, as it can rapidly result in blindness and even loss of the eye in severe, recalcitrant cases [2].

J.B. Miller, MD (✉)
Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA
e-mail: John_Miller@meei.harvard.edu

L.J. Haddock, MD
Department of Ophthalmology, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, Miami, FL, USA

J.W. Miller, MD
Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA
e-mail: Joan_Miller@meei.harvard.edu



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## 7.2 Intravitreal Medications

The advent of anti-vascular endothelial growth factor (anti-VEGF) medications has revolutionized the care of age-related macular degeneration, diabetic retinopathy, and retinal vein occlusions [3–5]. Currently, there are three anti-VEGF medications approved by the Food and Drug Administration (FDA) for ophthalmic use: pegaptanib (Macugen; Eyetech Pharmaceuticals), ranibizumab (Lucentis; Genentech), and aflibercept (Eylea; Regeneron Pharmaceuticals). In addition to these three FDA-approved medications, the off-label use of bevacizumab (Avastin; Genentech) has become widely adopted as an effective but lower-cost alternative for anti-VEGF therapy.

Prior to anti-VEGF medications, corticosteroids were first used intravitreally for the treatment of a variety of retinal diseases. While corticosteroids first saw a decline in use with the introduction of anti-VEGF mediations, there has been renewed interest lately as physicians examine combination or conversion therapy approaches [6]. Furthermore, sustained drug delivery is now being marketed with intraocular corticosteroids, such as the dexamethasone implant (Ozurdex of Allergan, Irvine, CA) among other emerging options.

## 7.3 Epidemiology

Fortunately, the incidence of endophthalmitis after intravitreal injections is very low for a procedure that is so common within ophthalmology. Meta-analyses have reported the rate of endophthalmitis after intravitreal injection of anti-VEGF medications to be between 1/2600 and 1/1530 (0.038–0.065 %) [7, 8]. In reviewing most major clinical trials from 2005 to 2012, Flynn's group [8] found an incidence of 0.056 %, identifying 197 cases of endophthalmitis from a total of 350,535 injections, or one case per 1779 injections.

Intravitreal corticosteroids have been presumed to produce a higher rate of endophthalmitis than anti-VEGF agents due to the immunosuppressive properties of the corticosteroid agents. However, there are limited data comparing the incidence of culture-confirmed endophthalmitis between these two treatments. Vanderbeek et al. [9] reviewed a large U.S. medical claims database with 387,714 anti-VEGF injections and 18,666 steroid intravitreal injections between 2003 and 2012. Their analysis identified endophthalmitis rates of 0.019 % for anti-VEGF injections and 0.13 % for corticosteroid injections. The odds ratio for endophthalmitis was 6.92 times higher after corticosteroid injections compared to anti-VEGF injections ($p < 0.001$) after controlling for demographics [9]. However, a limitation of this study (noted by the authors) was that culture results for endophthalmitis cases were not available, so the rate of culture-positive endophthalmitis in each group was not compared. This may have confounded the results, since data likely included noninfectious cases related to a sterile inflammatory response, which may be even more common after corticosteroid injections than anti-VEGF injections [10–12].

## 7.4 Clinical Presentation

Patients with post-injection endophthalmitis typically present with a red, painful eye and decreased vision within 5 days of their intravitreal injection. However, it is important to remember that not all patients will present with pain. A British review of 47 patients with endophthalmitis after injection in the United Kingdom found that reduced visual acuity (96 % of cases) was the most common presenting symptom, followed by pain/photophobia (73 %), and redness (49 %) [13]. Any unusual symptoms following an intravitreal injection should prompt urgent evaluation by the treating ophthalmologist. Most importantly, the absence of pain does not exclude endophthalmitis from the differential diagnosis.

## 7.5 Microbiology

The culture-positive rates of endophthalmitis are much lower than one might expect given a closed, small-volume system. Large case series and meta-analyses show positive cultures of only 52–59.6 % [7, 8, 13, 14]. The low yield of these cultures may occur due to difficulties in collecting and processing the vitreous sample. Others have suggested that less virulent strains that produce a lower grade endophthalmitis may be less likely to produce a positive culture [14]. Another possibility is that some cases treated as culture-negative endophthalmitis are not due to infection but rather represent a sterile inflammatory response to a component of the injected substance.

The most common organisms identified in culture-positive cases are coagulase-negative staphylococci (including *Staphylococcus epidermidis*) (63–65 %), followed by streptococci, most often viridans streptococci (30 %), *S. aureus* (0–4.9 %), and others (0–4 %), including *Enterococcus*, *Bacillus* species, and *Haemophilus* species [7, 8, 13, 14]. The rate of streptococcal endophthalmitis is higher in post-injection than in post-cataract endophthalmitis, possibly reflecting airborne contamination from oral flora during injection, as discussed below [15].

## 7.6 Preventive Measures

### *7.6.1 Topical Antibiotics*

The efficacy of topical antibiotic prophylaxis for intravitreal injections has been questioned. Topical antibiotics were widely used for prophylaxis in several of the early intravitreal injection clinical trials [16], but their use has been recently questioned [17]. Some studies have even reported a higher rate of postinjection endophthalmitis in patients using topical antibiotic prophylaxis [18, 19]. A large study by Storey et al. [18] found no benefit to using postinjection antibiotics. Furthermore,

as suggested by others, their data showed that topical antibiotic use may actually increase the risk of suspected endophthalmitis [18].

While topical antibiotics are no longer frequently employed, the topical antiseptic povidone-iodine is widely used for preventing endophthalmitis [20]. Additional work has shown that povidone-iodine does not increase antimicrobial resistance in the colonizing conjunctival flora of patients receiving anti-VEGF injections [21]. In contrast, repeated use of topical antibiotics for peri-injection prophylaxis does select for antibiotic-resistant bacteria in the conjunctival flora [22].

### *7.6.2 Eyelid Speculum*

The lid margins, eyelashes, and ocular surface contain numerous microbial species. The placement of a lid speculum can prevent contamination of the prepped injection site by free lashes or a blinking lid margin [23]. There is some concern that the speculum can induce lid squeezing and thus the secretion of infectious organisms from the lid margin. However, Friedman et al. found no change in conjunctival cultures after placement of a lid speculum [24]. While other techniques, such as bimanual retraction, have proven sufficient, the lid speculum is still common practice for intravitreal injections.

### *7.6.3 Facemask*

Upper respiratory flora, such as viridans streptococci, have been found on the injection site when either the ophthalmologist or patient talked during the procedure [25]. The use of a facemask can reduce the contamination of the injection site by respiratory flora [25]. However, the use of a face mask has not become routine across retina practices. As suggested by Schimel [26], many retina specialists require that neither the patient, assistant, nor ophthalmologist speaks during the injection procedure.

## 7.7 Management of Endophthalmitis

The fundamental components of management include a timely vitreous sample for culture and the administration of intravitreal antibiotics. The vitreous sample can be obtained in an office-based procedure with a tap and inject or via a vitrectomy in the operating room. Early vitrectomy should be considered in patients with poor vision or dense vitritis [27]. After obtaining the vitreous sample, intravitreal antibiotics are given. Severe cases may require a thorough vitrectomy to decrease the infectious load within the eye. Subsequent vitrectomy is also indicated when the clinical picture worsens after an initial tap and inject [28].

## 7.8 Visual Outcomes

There is limited data regarding visual outcomes after post-injection endophthalmitis. Part of the difficulty in evaluating visual outcomes in this patient population is the great variation in baseline visual acuity and baseline disease severity in patients requiring intravitreal injections. As a result, most studies have employed recovery of the pre-injection visual acuity for outcome analysis. The largest meta-analysis identified the causative organism as the most reliable predictor of visual outcome [8]. The more virulent strains such as streptococci are associated with worse visual recoveries.

## 7.9 Outbreaks of Endophthalmitis after Bevacizumab

Bevacizumab is a full-length humanized VEGF antibody that when used for intravitreal injections, needs to be repackaged by a compounding pharmacy under aseptic techniques into multiple syringes for extended storage and subsequent intraocular administration. A single vial is aliquoted into many single-use syringes, making bevacizumab much more affordable per unit dose than either ranibizumab or aflibercept. Recently, there have been outbreaks of endophthalmitis with repackaged bevacizumab due to syringes that were presumably contaminated during preparation at the compounding pharmacy. Goldberg et al. [29] reported 12 cases of endophthalmitis that developed after injection of compounded bevacizumab by the same physician in the Miami area. Microbiology results showed *Streptococcus mitis* and *Streptococcus oralis* in 10 of the cases, and also in seven of the unused syringes of the same medication lot prepared by the compounding pharmacy. The visual outcomes of these patients were very poor, and 1-year follow-up showed that seven patients (58 %) underwent enucleation/evisceration and only one patient (8 %) recovered pre-injection visual acuity [30]. An FDA review of the outbreak concluded that the contamination happened at the compounding pharmacy due to numerous problems in sterile technique [30]. Subsequently, Gonzalez et al. [31] have recommended increased oversight of compounding pharmacies to ensure strict adherence to the United States Pharmacopeia (USP) Chapter 797 requirements regarding sterility when repackaging a single vial of bevacizumab into multiple syringes.

## 7.10 Conclusions

Endophthalmitis after intravitreal injections is a rare, but devastating complication of this common eye procedure. Patients typically present within 5 days of their injection with decreased vision, pain, and redness. However, the absence of any one of these in the presence of other symptoms should not exclude the diagnosis of

endophthalmitis. Treatment consists of obtaining a vitreous sample and administering intravitreal antibiotics. Vitrectomy may be indicated in some cases. Preventive measures include the use of a lid speculum and topical povidone-iodine during the procedure, and clinicians may consider the use of masks or having all participants refrain from speaking.

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# Chapter 8
# Bleb-Related Endophthalmitis

**Tetsuya Yamamoto, Kiyofumi Mochizuki, and Akira Sawada**

## 8.1 Introduction

Glaucoma filtering surgery is a widely used surgical procedure for various types of glaucoma. Although the ocular hypotensive effect of the surgery is good, there is a risk of several sight-threatening complications, including bleb-related infection. Bleb-related infection includes blebitis and endophthalmitis and is further subdivided into early-onset type (<4 weeks) and late-onset type (>4 weeks). The latter type, which develops after the perioperative period, is more important because of its frequency and the chronic nature of glaucoma. Thus, we will focus on late-onset bleb-related infection in this chapter, including its clinical features, outcomes, common infectious agents, risk factors, prevention, and treatment.

## 8.2 Clinical Features

Bleb-related infection begins with bacterial conjunctivitis-like signs and symptoms, such as conjunctival hyperemia, discharge, foreign body sensation, etc. Slit-lamp microscopy reveals a yellowish-colored filtering bleb with moderate-to-severe conjunctival injection. In the case of endophthalmitis, an inflammatory reaction in the anterior chamber, often in the form of hypopyon, develops in addition to the conjunctival signs. Then, vitreous or retinal involvement is confirmed, in the most severe forms, via funduscopy, B-mode echography, and electroretinography. The more severe the inflammatory reaction, the more severe the visual disturbance and ocular pain. In some cases, vitreous involvement may occur within a few hours, especially in pseudophakic/aphakic eyes.

T. Yamamoto, MD, PhD (✉) • K. Mochizuki, MD, PhD • A. Sawada, MD, PhD
Department of Ophthalmology, Gifu University Graduate School of Medicine, Gifu, Japan
e-mail: mmc-gif@umin.net



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## 8.3 Prospective Studies

Because of its clinical significance, the Japan Glaucoma Society conducted two studies on bleb-related infection to investigate the incidence, risk factors, prognosis, clinical features, and causative infectious agents, in a prospective manner. These studies are the Collaborative Bleb-related Infection Incidence and Treatment Study [1, 2] (CBIITS) and the Japan Glaucoma Society Survey of Bleb-related Infection [3, 4] (JGSSBI).

The CBIITS was a prospective study where the enrollment period for new filtering surgery cases was 2 years and follow-up was done every 6 months for up to 5 years, with special attention to the development of bleb-related infection. Ophthalmological examinations were conducted at each follow-up according to a set protocol. When bleb-related infection was noted, additional examinations were conducted and the predetermined treatment was rapidly initiated, depending on the stage of the infection. Thirty-four institutions participated in the CBIITS. A total of 1098 eyes of 1098 cases, which were treated either with trabeculectomy or with combined surgery with mitomycin C, were analyzed. Bleb-related infection developed in 21 eyes.

The JGSSBI included a surveillance period of 5 years, with all patients having bleb-related infection consecutively registered from 82 medical centers in Japan and with collection of both clinical and microbial data. A total of 170 infections developed in 157 eyes of 156 patients that were seen in 45 institutions.

## 8.4 Classification

Bleb-related infection is subclassified into blebitis and endophthalmitis. Blebitis refers to infections confined to the conjunctiva and filtering bleb, even in the presence of a minor anterior chamber reaction. Bleb-related endophthalmitis refers to cases that include infection of the intraocular tissues and where an anterior chamber reaction is apparent and vitreous/retinal involvement may be present.

Azuara-Blanco and Katz [5] and Greenfield [6] proposed a staging system for bleb-related infection. Stage I denotes blebitis (Fig. 8.1); stage II denotes endophthalmitis where the main locus of infection is the anterior chamber and there is minimal or no posterior tissue involvement (Fig. 8.2); and stage III denotes endophthalmitis where the main locus of infection is in the posterior ocular tissues, with accompanying vitreous and/or retina involvement (Fig. 8.3).

The Japan Glaucoma Society modified this staging system by subclassifying stage III into stage IIIa and stage IIIb. Stage IIIa denotes mild involvement in the vitreous and stage IIIb denotes more advanced involvement [1–4]. Staging into category IIIa or IIIb is done mainly based on visibility of the fundus and vitreous opacity detected by B-mode echography.

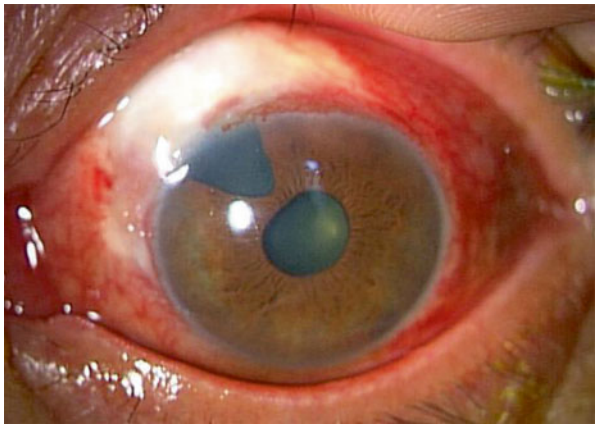

**Fig. 8.1** Stage I bleb-related infection or blebitis. Inflammation is confined to the conjunctival region

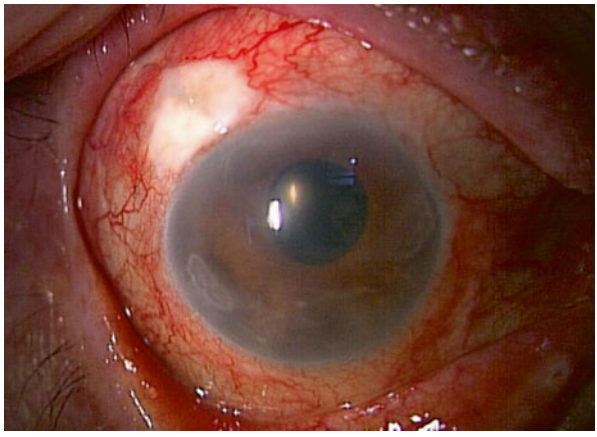

**Fig. 8.2** Stage II bleb-related infection or early bleb-related endophthalmitis. The main locus of inflammation is in the anterior chamber

## 8.5 Incidence

According to the CBIITS [2], the incidence of bleb-related infection was calculated by a Kaplan-Meier method to be 2.2 ± 0.5 % (cumulative incidence ± standard error) at the 5-year follow-up in cases that underwent trabeculectomy or trabeculectomy/PEA/IOL with mitomycin C. It was estimated to be 3.9 ± 1.0 % at the 5-year follow-up when only well-functioning blebs were included. The incidence of endophthalmitis comprising only stage II and III cases was also reported to be 1.1 ± 0.3 % at the 5-year follow-up. Cases with a positive history of bleb leakage and those without leakage showed an incidence of bleb-related infection of 7.9 ± 3.1 % and 1.7 ± 0.4 % ($p = 0.000$: log-rank test), respectively, at the 5-year follow-up.

The incidence of bleb-related infection is also reported elsewhere. In the Collaborative Initial Glaucoma Treatment Study, Zahid et al. [7] reported a 5-year incidence of blebitis and endophthalmitis of 1.5 % and 1.1 %, respectively, in 285

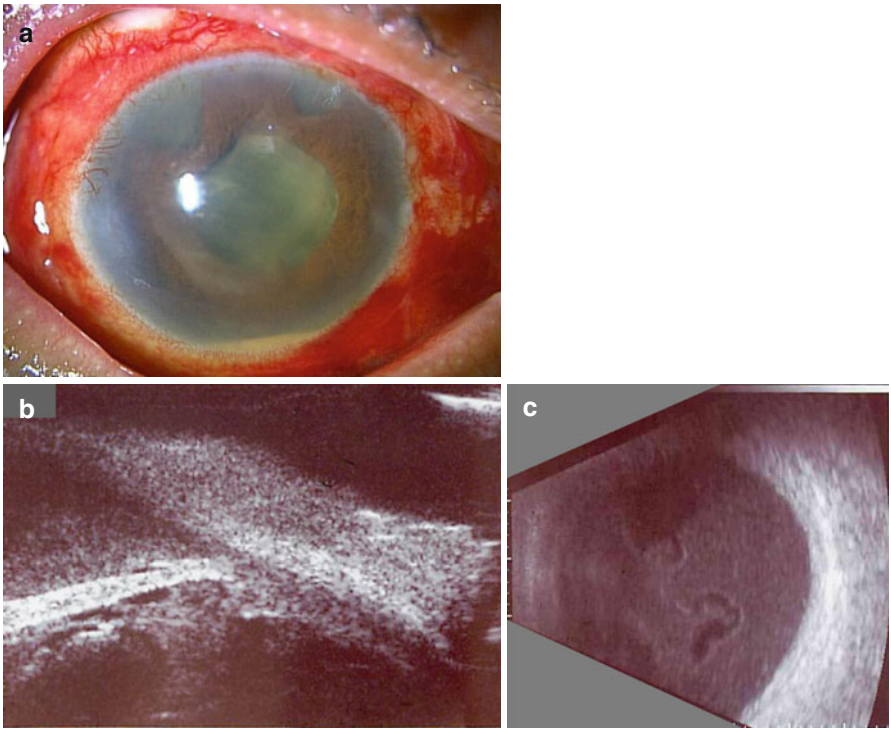


**Fig. 8.3** Stage III bleb-related infection or late bleb-related endophthalmitis. The main locus of inflammation is in the vitreous or retina. A pseudophakic eye. (**a**) Anterior segment photography; (**b**) ultrasound biomicroscopic view; (**c**) B-mode echography

patients, among which 57 % had used 5-fluorouracil adjunctively with trabeculectomy. In the Tube Versus Trabeculectomy Study, Gedde et al. [8] reported an incidence of 4.8 % in 105 eyes at 5-year follow-up following trabeculectomy. Additionally, Solus et al. [9] reported a 1.2 % incidence per year for limbus-based surgery and a 0.3 % per year incidence for fornix-based surgery for the first 4 years after surgery.

## 8.6 Microbiology

Various bacteria have been isolated in bleb-related infections, and many are suspected to be causative agents. Among the most commonly reported isolates are *Streptococcus* species, *Staphylococcus aureus*, and coagulase-negative staphylococci (Table 8.1) [3, 10–16]. The severity of a bleb-related infection can vary markedly as a function of the type of bacteria. In the early stages, coagulase-negative staphylococci (*S. epidermidis* included), *Corynebacterium*, etc. are commonly isolated. In the late stages, *Streptococcus* species, *S. aureus*, coagulase-negative staphylococci, *H. influenzae*, and *Enterococcus* species are more frequently isolated. *Streptococcus* species are frequently isolated from the conjunctiva in eyes with blebitis [17].

**Table 8.1** Microbiology in bleb-related endophthalmitis, from the literature

| Authors | Kangas et al. [13] | Waheed et al. [14] | Song et al. [15] | Jacobs et al. [16] | Yamamoto et al. [3] | Total No. (%) |
|---|---|---|---|---|---|---|
| Year | 1997 | 1998 | 2002 | 2011 | 2013 | |
| Bacteria | | | | | | |
| *Streptococcus* spp.[a] | 13 | 8 | 16 | 21 | 17 | 75 (36)[a] |
| *Staphylococcus aureus* | 0 | 13 | 4 | 0 | 7 | 24 (11) |
| Coagulase negative staphylococci | 5 | 12 | 6 | 9 | 7 | 39 (18) |
| *Enterococcus* spp. | 2 | 0 | 9 | 6 | 3 | 20(9) |
| *Haemophilus influenzae* | 5 | 2 | 1 | 0 | 3 | 11(5) |
| Miscellaneous | 3 | 7 | 3 | 22 | 7 | 42 (20) |
| Total number of cases | 28 | 42 | 39 | 58 | 44[b] | 211 |

*spp* species

[a]Streptococci were further identified in studies by Kangas, Waheed, and Song, as follows: viridans streptococci (23 of 37 cases, 62 %), *Streptococcus pneumoniae* (7 of 37 cases, 19 %), beta-hemolytic streptococci (Groups A, B, G) (7 of 37 cases, 19 %)

[b]Stage II and stage III (endophthalmitis) in the Yamamoto study. Culture results reflect intraocular cultures except in the Yamamoto study, which also includes conjunctival (bleb) cultures. Including only intraocular cultures in the Yamamoto study: *Streptococcus* species (15), *S. aureus* (1), coagulase-negative staphylococci (3), *Enterococcus* species (3), *Haemophilus influenzae* (2), miscellaneous (5)

The visual prognosis is poor when *Streptococcus* species, *Enterococcus* species, *S. aureus*, and gram-negative bacilli are the causative agents, while it is considerably better in cases with coagulase-negative staphylococci.

## 8.7 Outcome

The outcome of a bleb-related infection is related to the virulence of the bacteria and the stage of the infection. The JGSSBI [4] found that the visual acuity dropped by an average of 0.504 logMAR units at 12-month post-infection, with a patterned variation that reflects the infection's stage. For example, a stage III infection with a positive bacterial culture was significantly associated with a worse visual outcome.

The visual outcome of bleb-related infection is poor in endophthalmitis and in cases of stage II or III infection. Table 8.2 indicates the visual outcomes of such cases reported in the literature. A post-infection visual acuity of 20/400 or better was reported in 22–63 % of cases in bleb-related endophthalmitis [4, 12, 13, 18, 19]. The incidence of no light perception was reported to be 35 % at 12 months after treatment and that of visual loss, defined as at least 5 Snellen lines, was 64 % [20]. An average increase in the logMAR of 1.42 units was also reported following bleb-related endophthalmitis [18]. The incidence of blindness caused by bleb-related

**Table 8.2** Visual acuity ≥20/400 after bleb-related endophthalmitis, from the literature

| Authors | Ciulla et al. [12] | Kangas et al. [13] | Song et al. [15] | Yamamoto et al. [4] | All |
|---|---|---|---|---|---|
| Year | 1997 | 1997 | 2002 | 2013 | |
| Total no. of patients | 32 | 32 | 49 | 30[a] (18) | 143 |
| No. of final VA ≥20/400 | 7 | 15 | 26 | 19 (10) | 67 |
| Percentage | 22 % | 47 % | 53 % | 63 % (56 %) | 47 % |

[a]Stage II and stage III. Parentheses: stage III only

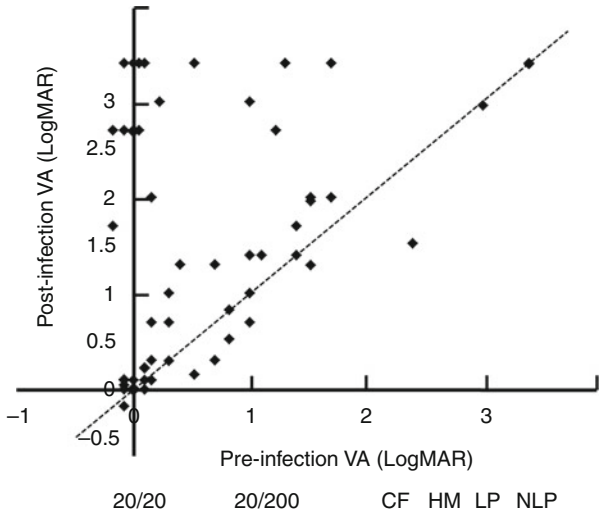


**Fig. 8.4** Visual acuity after bleb-related endophthalmitis (stages II and III). From updated JGSSBI data

infection was estimated to be 0.24–0.36 % in the 5 years following filtering surgery with mitomycin C for open-angle glaucoma, where blindness was defined as an eye with a visual acuity of less than 20/400 [21]. Even with the application of modern treatment strategies, including intensive antibacterial agents and vitreoretinal surgery, the visual outcomes in bleb-related endophthalmitis remain relatively poor. The JGSSBI indicated that the mean increase in the logMAR was 0.140, 0.440, 1.099, and 1.122 at 12-month post-infection for stage I, II, IIIa, and IIIb infections, respectively (Fig. 8.4) [4]. Thus, the visual outcomes in cases where the infection is confined to the bleb region, or in the case of blebitis, are superior to that in cases of endophthalmitis.

The morphology of a filtering bleb is negatively affected by a bleb-related infection. Endophthalmitis, in particular, worsens the bleb morphology, while the effect of blebitis is less damaging. As a result, the IOP increases accordingly after the infection has subsided. The JGSSBI demonstrated that IOP did not change in stages

I and II and that it increased by a mean of 2.7 and 6.6 mmHg at 12-month post-infection for stages IIIa and IIIb, respectively [4]. Being stage III was a significant risk factor for poor IOP control. In other literature, a mean IOP increase of 1.2 mmHg was reported following endophthalmitis [22], while the IOP was uncontrolled (>21 mmHg) in 11 % of bleb-related infections [15].

## 8.8 Risk Factors

The major factors that are significantly associated with greater risk for the development of bleb-related infection are the use of antimetabolites, an inferiorly located bleb, and the presence of bleb leakage [23–25]. Other reported risk or associated factors include, but are not limited to, bleb morphology, sex, age, systemic diseases such as diabetes mellitus, seasons, history of intraocular surgery, status of the lens, ethnicity, history of conjunctivitis and blepharitis, and the use of contact lens.

The use of antimetabolites, such as mitomycin C and 5-fluorouracil, increases the risk of developing bleb-related infection. In cases without the use of such agents, the rate of bleb-related infection was reported to be 0.2–1.5 % [26, 27], whereas it was 1.9–5.7 % following trabeculectomy with 5-fluorouracil [28, 29] and 1.6–4.8 % after trabeculectomy with mitomycin C [8, 22].

A couple of bleb-associated parameters are known to be associated with an increased risk of bleb-related infection [24, 25]. An inferiorly located bleb is one of them. It tends to be exposed, and discharge may be found in the inferior region, which is speculated to be related to the high incidence. Trabeculectomy is now rarely performed in the inferior half since the advent of glaucoma drainage devices, so this will not be a strong risk factor in the future. Avascular bleb is another risk factor. They may occur after antimetabolite surgery which alters the physiological barrier mechanisms of the conjunctival tissues. Bleb leakage is also a significant risk factor. A positive history of bleb leakage was associated with a 4.71-fold increase in the incidence of infection in the CBIITS [2]. Thus, repair of any leaking bleb should be considered, even though it can be difficult and may increase the IOP in certain cases. The type of conjunctival flap used may also be related to the incidence and timing of bleb-related infection. A limbus-based conjunctival flap, instead of a fornix-based flap, was associated with more bleb-related infections in several reports [9, 30].

Although the findings are not consistent [10, 22], some studies reported that male patients and younger patients are at higher risk for infections [2, 31]. One study reported that diabetes mellitus and a recently treated episode of blebitis (average 9 weeks earlier) were significant risk factors for bleb-related endophthalmitis [32]. Seasons may have some effect on bleb-related infection. In a study of risk factors of bleb-related infections in Israel, winter season was found to increase the risk [33]. However, our study from Japan, by contrast, found that bleb-related infection increased in the transition from spring to summer [34]. It may be the case that global differences in the nature of the seasons may account for difference in the seasonal variation of these infections.

Intraocular surgery and bleb repair procedures may also be related to the development of bleb-related infection [22, 35]. Vitreous involvement may develop earlier in pseudophakic or aphakic eyes as compared with phakic eyes.

Obstruction of the nasolacrimal duct is also a known risk factor for some ocular infections. However, at least one study did not support the notion that bleb-related infection is associated with such obstructions [21].

## 8.9 Prevention

Since the prognosis is not always satisfactory, prevention of bleb-related infection must be a priority. Routine use of prophylactic antibacterial therapy is not recommended [22, 36]. Patient education on bleb-related infection and habitual carrying of antibacterial eyedrops are the mainstays. Post-trabeculectomy patients should be well educated on the risk of bleb-related infection, preventative measures, and how to respond to signs of infection and related emergencies. The emergency phone number of an ophthalmology clinic should be provided to each patient. In particular, they should be instructed to immediately seek medical attention if they notice a yellowish discharge, moderate-to-severe conjunctival injection, or any other early sign of bleb-related infection. They may start antibacterial eyedrops if they cannot immediately see an ophthalmologist.

When frank bleb leakage is noticed, surgical repair may be indicated if the leakage does not disappear spontaneously.

## 8.10 Treatment

Treatment of bleb-related infection consists of antibacterial medication and vitreous surgery. Before initiating treatment, the eye must first be evaluated and the infection staged. Below is an example of the management of bleb-related infection as adopted in the CBIITS [1, 2]:

### *8.10.1 For Blebitis or Stage I Infection*

Initiate frequent dosing (once every hour) with topical levofloxacin 0.5 % and cefmenoxime hemihydrochloride 0.5 %, ofloxacin ophthalmic ointment at bedtime, and subconjunctival injections of vancomycin hydrochloride (25 mg in 0.5 ml) and ceftazidime (100 mg in 0.5 ml).

### 8.10.2 For Stage II Infection

In addition to the above-described use of eyedrops and ophthalmic ointment, initiate intracameral injections of vancomycin hydrochloride (1 mg in 0.1 ml) and ceftazidime (2.25 mg in 0.1 ml) and systemic antibiotics (type/dose at the discretion of clinicians). The intracameral injection may be repeated 36 h after the first injection, in cases where it was not initially effective.

### 8.10.3 For Stage IIIa Infection or Cases with Mild Vitreous Involvement

In addition to the above-described use of eyedrops and ophthalmic ointment, initiate intravitreal injections of vancomycin hydrochloride (1 mg in 0.1 ml) and ceftazidime (2.25 mg in 0.1 ml) and systemic antibiotics (type/dose at the discretion of clinicians). A corticosteroid, either systemic or local, may be used after sufficient antibiotic therapy. The intravitreal injection may be repeated 36 h after the first injection, in cases where it was not initially effective.

### 8.10.4 For Stage IIIb Infection or Cases with More Advanced Vitreous Involvement

Treatment with immediate vitreous surgery with intravitreal irrigation of vancomycin (100 mg in 500 ml) and ceftazidime (200 mg in 500 ml), plus systemic antibiotics (type/dose at the discretion of clinicians), was used in the CBIITS, in addition to the above-described eyedrops and ophthalmic ointment. Other centers use intravitreal injections of antibiotics, such as vancomycin plus ceftazidime, at the conclusion of vitrectomy, rather than intravitreal irrigations. A corticosteroid, either systemic or local, may be used after sufficient antibiotic therapy. One retrospective study reported improved visual acuity outcomes in patients who received intravitreal dexamethasone as part of their treatment versus those who did not [37].

Since the prognosis of vitreous surgery for bleb-related endophthalmitis is not always satisfactory, it should only be done on an emergency basis (Fig. 8.5). Irrigation with an appropriately titrated antibacterial agent was used in the CBIITS, but other centers use intravitreal injections of antibiotics (such as vancomycin plus ceftazidime) rather than intravitreal antibiotic irrigations.

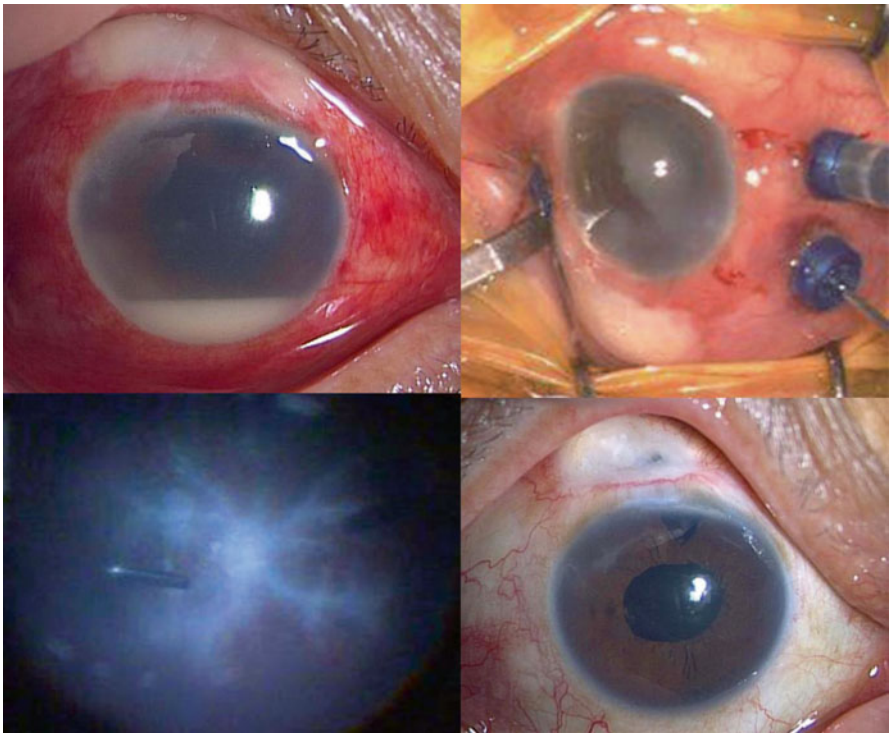

**Fig. 8.5** A case of *Streptococcus* bleb-related endophthalmitis treated with vitreous surgery. *Top left*: anterior segment photography at presentation. *Top right*: intraoperative photo. *Bottom left*: whitened vessels confirmed intraoperatively. *Bottom right*: postoperative photo. Visual acuity was HM at presentation and 20/50 at final. Intraocular pressure was 30 mmHg at presentation and 10 mmHg at final

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# Chapter 9
# Post-traumatic Endophthalmitis

**Neelakshi Bhagat, Xintong Li, and Marco A. Zarbin**

## 9.1 Introduction

Endophthalmitis is a severe but uncommon complication of penetrating ocular trauma noted in 2–7 % of open-globe injuries (OGI) in recent studies [1–4]. Infection of the eye after injury, a form of exogenous endophthalmitis referred to as post-traumatic endophthalmitis, makes up 10–31 % of all cases of endophthalmitis [5–7].

Eye injury is classified using standard criteria developed by the Ocular Trauma Classification System [8] (Fig. 9.1). An OGI involves a full-thickness defect in the cornea or sclera either due to a rupture or laceration. Ruptures are due to blunt trauma causing a rapid increase in intraocular pressure resulting in a defect in the globe wall. Lacerations, which arise from injury with a penetrating object, are further categorized as penetrating or perforating, and the presence of an intraocular foreign body (IOFB) is classified separately. Penetrating injuries are ones in which there is an entrance wound, while perforating trauma is defined by the presence of separate entrance and exit wounds.

N. Bhagat, MD, MPH, FACS (✉) • M.A. Zarbin, MD, PhD
Department of Ophthalmology, Rutgers New Jersey Medical School,
Institute of Ophthalmology and Visual Science, Newark, NJ, USA
e-mail: bhagatne@njms.rutgers.edu

X. Li
Rutgers New Jersey Medical School, Newark, NJ, USA



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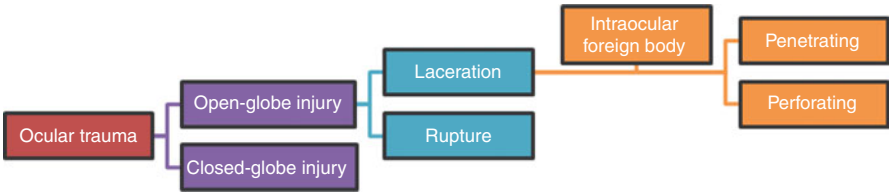


**Fig. 9.1** Classification of ocular trauma

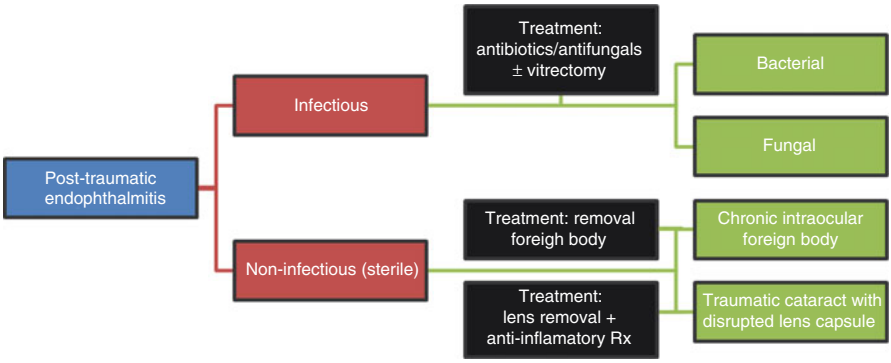


**Fig. 9.2** Types of post-traumatic endophthalmitis

### *9.1.1 Epidemiology*

Males and young persons are overrepresented in cases of eye trauma [9, 10]. In almost all large-scale recent epidemiologic studies worldwide, males are involved in 74–88 % of cases [11–16]. In one study conducted in India, the average patient with post-traumatic endophthalmitis was 22 years old, younger than for postoperative (52 years) or endogenous (31 years) endophthalmitis. In a study from Iran, the average age of infectious cases due to trauma was 19 years old [2]. A higher incidence of post-traumatic endophthalmitis is reported in OGI cases in children (5–54 % [17–22]) versus adults (1–18 % [21, 23–32]). In children, trauma is the number one cause of endophthalmitis [33].

### *9.1.2 Classification*

Post-traumatic endophthalmitis can be infectious or non-infectious (Fig. 9.2), with IOFBs and retained crystalline lens fragments being commonly implicated in non-infectious, or reactive, cases. This chapter will focus on infectious post-traumatic endophthalmitis.

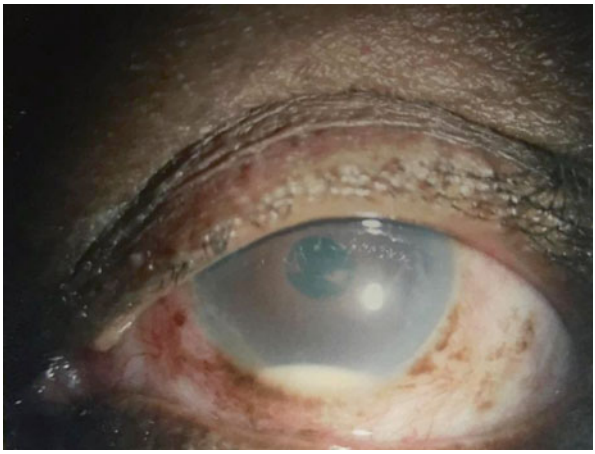

**Fig. 9.3** External photograph of a patient presenting with hypopyon and endophthalmitis after trauma

## 9.2 Clinical Presentation and Risk Factors

Signs of post-traumatic endophthalmitis are similar to those of endophthalmitis due to other etiologies. Purulent exudative discharge, eyelid edema, chemosis, corneal edema, anterior chamber reaction, hypopyon (Fig. 9.3), and vitritis are signs of intraocular infection [23, 34]. Cases with delayed onset often have intraocular inflammation and evidence of an apparently healed eye injury, but no purulent discharge, chemosis, or lid edema. Pain, poor vision, and postoperative inflammation are normal findings after eye injury that could also signal early endophthalmitis, making initial diagnosis of endophthalmitis difficult. Disproportionate pain or vision loss following trauma and an increase in pain or vision loss after repair are classic symptoms for post-traumatic infection cases [35]. Certain characteristics of the history and examination, if present, may point the physician towards specific microorganisms causing post-traumatic endophthalmitis. Corneal ring abscess is highly suggestive of *Bacillus*, while gas bubbles in the anterior chamber, amaurosis, or green-brown hypopyon indicates *Clostridium* [34, 36]. A fungal etiology is more likely if onset is subacute, e.g., over a few weeks after injury, with minimal pain, or if the anterior chamber or vitreous contains white clump-like or filamentous opacities [34, 37]. However, bacterial etiologies must still be considered for all acute, subacute, and chronic presentations.

A thorough history and clinical examination is paramount for all patients with suspected endophthalmitis, recognizing that the injury may have occurred in the recent but not immediate past. One should also obtain information regarding the mechanism of injury (which may heighten suspicion for an IOFB), the location of the patient at the time of injury (rural injuries and injuries with contaminated instru-

ments are associated with increased risk; work injuries may have legal implications), and ascertainment of whether the patient was wearing protective eye wear and/or contact lenses at the time of injury (relevant both from the standpoint of risk of IOFB and legal issues). Significant risk factors for endophthalmitis after trauma include delay in treatment of the OGI, rural setting of trauma, IOFB, and lens capsule disruption. Numerous retrospective studies have evaluated these risk factors:

### *9.2.1 Delay in Treatment*

*Primary Closure* Primary surgical closure of the globe beyond 24 h [32, 38] or 36 h [39] after presentation is associated with increased risk of endophthalmitis independent of IOFB presence.

*IOFB Removal* A large-scale study based on the National Eye Trauma System Registry suggested an increased incidence of endophthalmitis in eyes with retained IOFB that underwent surgical intervention after 24 h compared to within 24 h (13.4 % vs. 3.5 %) [40]. Recent studies generally confirm this association [41], but a study of 70 eyes that underwent a median delay of 21 days before IOFB removal after injury in combat during Operations Iraqi Freedom and Enduring Freedom but with prompt open-globe repair and antibiotic prophylaxis revealed no cases of endophthalmitis [42]. Another study of ocular injuries in the British Armed Forces confirmed similar findings [43]. In combat settings, high-velocity projectiles (as a result of explosions or gunshots) may self-sterilize before they enter the eye and thus fail to increase the risk of endophthalmitis. The cases in these two retrospective studies also underwent timely globe closure with antibiotic prophylaxis, which may also have contributed to the complete absence of endophthalmitis cases.

*Prophylactic Antibiotics* Use of prophylactic intravitreal antibiotics remains controversial. A prospective randomized case-controlled trial performed in Iran on the utility of injection of intravitreal antibiotics in addition to intravenous antibiotics showed a decrease in incidence of endophthalmitis only in eyes with an IOFB present [45].

### *9.2.2 Trauma Characteristics*

*Rural Setting* The incidence of endophthalmitis is generally increased in patients presenting after eye trauma from a rural setting, as shown in a retrospective review of OGI cases from Australia [26] and from Saudi Arabia [46]. This finding may be due to an increased risk of acquiring an IOFB contaminated with soil or organic matter and a higher chance of infection with the more virulent *Bacillus*, *Clostridium*, and fungal species (see Sect. 9.3.2).

**Table 9.1** Characteristics of nonmetallic IOFBs on imaging [48]

| IOFB type | CT | T1-/T2-MRI | GE-MRI |
|---|---|---|---|
| Glass | Detectable | Signal void | |
| Windshield | | Irregular | Enlarged |
| Bottle | | Smooth | Not enlarged |
| Stone | Detectable | Signal void with surrounding hyperintensity | |
| Gravel | | Subtle surrounding hyperintensity | Void, not enlarged |
| Concrete | | | Void, enlarged |
| Porcelain | | | Surrounding white ring, enlarged |
| Graphite | | | Surrounding white ring, enlarged >2× |
| Plastic | Undetectable | Signal void | |
| CR39 | | | Slightly enlarged |
| Plastic | | | Not enlarged |
| Organic | Undetectable | Signal void with surrounding hyperintensity | |
| Wood | | | Slightly enlarged |
| Thorn | | | Enlarged |

*IOFB* intraocular foreign body, *CT* computed tomography, *MRI* magnetic resonance imaging, *GE* gradient echo

### *9.2.3 Wound Characteristics*

*Lacerations* A study of 4968 eyes with OGI showed that the presence of a laceration, which includes IOFB, penetrating, and perforating injuries, versus globe ruptures was an independent risk factor for endophthalmitis (odds ratio of 2.87) [32].

*IOFB* Studies confirm that the presence of an IOFB is associated with an increased risk of endophthalmitis, especially if it is contaminated with soil or organic matter. This correlation was recently re-demonstrated in retrospective case series reviewing OGI cases in Romania [44] and another in Iran [2]. Imaging may be needed to rule out an IOFB, with non-contrast CT (fine cuts) currently being the most sensitive modality for metallic IOFBs, which comprise the majority of cases [47]. A masked study using porcine eyes with various nonmetallic IOFBs revealed that MRI may be used to detect glass, stone, plastic, and organic IOFBs [48]. The distinguishing features of each on T1-/T2-MRI and gradient-echo sequences as assessed algorithmically are listed in Table 9.1. Clinicians must remember to definitively rule out a metallic IOFB with CT (as well as associated scout X-ray films) before the patient undergoes MRI; tiny pieces of metal undetectable on CT are generally regarded as safe for MRI [48].

*Dirty Wound* A dirty wound, defined as a wound contaminated with soil or organic matter, has been associated with an increased risk of endophthalmitis independent of whether or not the injury occurred in a rural setting. This association was present even on multivariate analysis in the OGI series from Australia (odds ratio of 5.3) [26] and from Saudi Arabia (odds ratio of 11.6) [46].

### *9.2.4 Associated Conditions*

*Lens Capsule Disruption* A study from Australia showed that traumatic endophthalmitis is 12.4 times more likely if associated with breach of the lens capsule [1], which is consistent with other reports [26, 30, 40]. The biological basis of this association is not clear but may involve lens cortex-facilitated growth of bacteria. However, extensive reactive inflammation due to retained lens fragments, termed phacoanaphylactic endophthalmitis, may be difficult to differentiate from infectious endophthalmitis. In these cases, biopsies of the aqueous and vitreous may reveal zonal granulomatous inflammation with polymorphonuclear leukocyte infiltration surrounding the lens fragments [49–51].

It remains controversial whether other factors such as intraocular tissue prolapse, wound length, and wound location increase the risk of endophthalmitis. Some studies suggest an increased risk with uveal or vitreous prolapse [45], whereas other studies deny that association [4, 32, 44]. The effect of wound length is also uncertain; larger wounds have traditionally been associated with a greater risk of endophthalmitis [26, 39], but some studies show otherwise [4, 38]. Furthermore, the effect of wound location on the development of endophthalmitis remains a topic of debate; some studies indicate an association with anterior wounds [4, 32, 38], while others suggest a positive correlation with posterior IOFB or wound [3, 25]. Researchers have hypothesized that these three variables may be interrelated to each other and affect the incidence of endophthalmitis. For instance, a larger wound has a larger surface area for intraocular tissue contamination, while increasing the risk of tissue prolapse. More studies are needed to assess the effects of these factors on endophthalmitis.

Intravitreal antibiotic prophylaxis at presentation following initial trauma should be carefully considered if one or more of the risk factors listed above are present (see Sect. 9.6).

## 9.3 Diagnosis

### *9.3.1 Early Evaluation*

| Steps in initial management |
|---|
| Biopsy |

| Steps in initial management |
|---|
| Vitreous |
| Wound |
| IOFB |
| Laboratory tests |
| Bacterial and fungal cultures |
| Gram and KOH/calcofluor stain |
| PCR |
| Start empiric antibiotic therapy |

Once a clinical diagnosis of endophthalmitis is made, the clinician should send samples of any purulent discharge, along with samples of aqueous and/or vitreous for stains and cultures. Samples should be sent for Gram stain and fungal stain (calcofluor white or KOH), routine aerobic culture (e.g., chocolate agar, blood agar, thioglycollate broth), anaerobic culture, and fungal culture (Sabouraud agar). Cultures should be obtained before initiating antibiotic therapy if possible. If an IOFB is present in the setting of presumed infection, an attempt should be made to remove the IOFB emergently and to treat the patient with intravitreal and systemic antibiotics. It is important to note that endophthalmitis is a clinical, not a laboratory, diagnosis. Thus, negative cultures cannot rule out endophthalmitis, nor can positive cultures make the diagnosis in the absence of clinical suspicion [52, 53]. The utility of cultures is simply to tailor antibiotic therapy after the diagnosis is made.

In recent years, polymerase chain reaction (PCR) testing for the identification of microbes using vitreous fluid in cases of endophthalmitis has shown increasing clinical utility, with sensitivities of 95–100 % compared to 38–53 % for culture [54–57]. PCR tests for the presence of bacterial 16S or fungal 18S/28S rDNA by sequencing either against pre-selected species or against a database for broad-spectrum identification. Molecular techniques used to diagnose endophthalmitis are discussed in Chap. 4.

### *9.3.2 Microbiology*

Bacterial endophthalmitis typically presents acutely, with *Bacillus* as the most fulminant, while fungal infections are more subacute. Gram-positive bacteria are the most common cause of post-traumatic endophthalmitis, followed by gram-negative bacteria (10–33 % [21, 58–60]), and then fungi. *Pseudomonas* is the most likely cause in gram-negative cases, with *Candida* the number one cause for fungal post-traumatic endophthalmitis in some series [21, 34, 61]. The frequency of various isolates varies somewhat by locale. In regions with tropical climates such as China, India, and southern Florida, fungi and especially molds cause a higher percentage of post-traumatic cases. In a series from China, fungi caused 17 % of 347 culture-positive cases, with two-thirds of the fungal cases due to molds, mainly *Aspergillus* and *Fusarium* [21]. One-sixth of the fungal endophthalmitis cases were mixed

**Table 9.2** Association of injury characteristics with microbiological etiology of culture-positive cases of post-traumatic endophthalmitis

| Injury characteristic | Microbiology |
|---|---|
| Soil contaminated | *Clostridium*, *Bacillus,* fungal |
| Organic matter | Fungal |
| Rural setting | Polymicrobial, *Bacillus* |
| Injuries from orthodontic procedures or headgear (very rare) | *Streptococcus*, polymicrobial |

infections with gram-negative bacilli. In a series from India of 581 patients with post-traumatic endophthalmitis, *Bacillus*, streptococci, and coagulase-negative staphylococci were the most common organisms in that order, while fungi caused 9 % of cases and 95 % of the fungi were molds [61].

In adults, *Staphylococcus epidermidis* is one of the most common organisms isolated (16–45 % [21, 61–63]) and, along with other coagulase-negative staphylococci, is associated with the best prognosis [64]. *Streptococcus* species, particularly viridans streptococci, are the most common etiologies in several pediatric series, causing roughly half of cases [65, 66], while coagulase-negative staphylococci are second most common. Infection with *Bacillus, Clostridium,* and gram-negative organisms is associated with a poor prognosis, with *Bacillus* infection being especially grim. *Bacillus* is a relatively common cause of post-traumatic endophthalmitis in adults, accounting for 9–45 % of cases [21, 61–63, 67]. Both *Bacillus* and *Clostridium* have a high likelihood of rapid progression to panophthalmitis, frequently despite appropriate aggressive management.

Associations between characteristics of the primary injury with the microbiological etiologies of ensuing endophthalmitis are found in Table 9.2.

## 9.4 Treatment

### *9.4.1 Medical*

After initial clinical evaluation, a rigid shield should be placed over the infected eye and the patient ordered nothing by mouth (NPO). To reduce the risk of *Clostridium tetani* wound infection, patients with open-globe injuries should receive a tetanus vaccine if they have not received one in 5 or more years, or if they have never received one. Most children and adults in the United States have completed at least three prior tetanus vaccinations, with the first four doses given in infancy, the fifth at ages 4–6, and the sixth at ages 11–12; repeat "booster" shots are then due every 10 years although many adults do not keep up with that booster shot schedule. There are several types of tetanus toxoid-containing vaccines, but all are effective against tetanus: Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) or Td (tetanus and diphtheria toxoid) are used for wound prophylaxis for ages seven

and older; DTaP (diphtheria and tetanus toxoids and acellular pertussis) is given to children younger than seven who qualify for tetanus vaccination. Patients with open-globe injuries who have received fewer than three tetanus vaccinations (ever), or whose history of tetanus immunization is unknown, should receive Tdap or Td (children younger than seven who meet these qualifications should receive DTaP instead). Tdap or Td should also be given if the patient with an open-globe injury has had three or more tetanus vaccinations in the past but whose last vaccination was 5 or more years ago. Tdap is preferred to Td for ages 11 and older in this circumstance if the patient hasn't had Tdap before [68, 69]. Children under age seven whose last tetanus vaccine was 5 or more years ago would receive DTaP. Patients with incomplete (<3 doses) or unknown history of tetanus immunization and an open-globe injury can receive human tetanus immune globulin as passive immunization, in addition to receiving the tetanus toxoid-containing vaccine [70, 71].

If OGI is diagnosed with endophthalmitis, primary globe repair should be performed expeditiously along with removal of the IOFB, if present. In a patient presenting with new-onset endophthalmitis after primary globe repair, it is important to

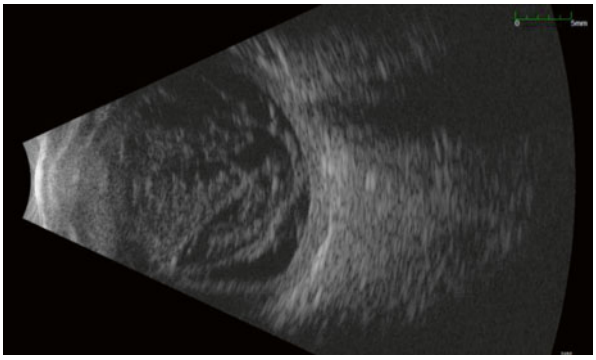

**Fig. 9.4** B-scan ultrasonography showing vitreous opacities in an eye with post-traumatic endophthalmitis

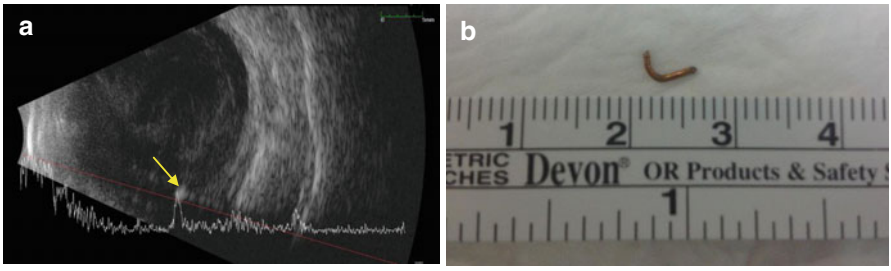


**Fig. 9.5** (**a**) B-scan ultrasonography of an eye with post-traumatic endophthalmitis suspicious for an intraocular foreign body; A-scan shows the foreign body as a hyperintense area with high reflectivity (*yellow arrow*) **(b).** The foreign body, a metallic nail measuring 4.5 mm, was later removed from the same eye

reassess the patient to consider reimaging the orbit and globe for the presence of an occult IOFB (see Sect. 9.2.3 IOFB, and Table 9.2). B-scan ultrasonography can be used to visualize the posterior segment for anatomic integrity [72] (Fig. 9.4) and IOFBs (Fig. 9.5) using extreme caution to avoid excess pressure on the eye. Ultrasound biomicroscopy may reveal the presence of an occult IOFB in the anterior segment.

Once diagnosed with acute bacterial endophthalmitis, the patient should emergently receive injections of intravitreal vancomycin 1 mg/0.1 mL and ceftazidime 2.25 mg/0.1 mL as empiric treatment, while awaiting results of culture. Use of empiric aminoglycoside in place of the ceftazidime may be considered but is usually avoided due to concerns for retinal toxicity [73]. Such an injection may be necessary if culture results show a gram-negative bacterium resistant to ceftazidime. Pars plana vitrectomy (PPV) is often necessary to rapidly clear the infection and improve outcomes, as discussed in the next section.

The adjunctive role of systemic antibiotics is unknown in treating post-traumatic endophthalmitis, but these antibiotics may prolong therapeutic antibiotic intraocular levels so are usually added for this potentially devastating infection. For systemic therapy, we recommend intravenous vancomycin plus either ceftazidime or a quinolone (e.g., ciprofloxacin or levofloxacin). Quinolones may be given orally in patients with adequate absorption. Topical antibiotics such as vancomycin and a quinolone should also be instilled at frequent intervals on the infected eye (e.g. hourly). This regimen is selected because most organisms implicated in post-traumatic bacterial endophthalmitis are reported to be sensitive to one or both of these antibiotics [21, 61, 74]. In addition, topical quinolones (especially fourth-generation quinolones) penetrate the cornea to achieve concentrations in the aqueous that are above the minimum inhibitory concentration for many bacteria. Topical ceftazidime may be substituted for topical quinolone, but data on intraocular penetration of topical ceftazidime is lacking [75]. Eyes with a high clinical suspicion of *Bacillus* may also receive intravitreal clindamycin 1 mg/0.1 mL injection, although vancomycin should be effective against nearly all *Bacillus* isolates [36]. Intravitreal preparations of ciprofloxacin have been used experimentally in rabbits but not in humans [21, 76, 77]. A single case report of successful use of intravitreal moxifloxacin has been described in a patient with post-traumatic endophthalmitis due to a rare gram-negative bacillus (*Ochrobactrum*) [78]. Systemic quinolones achieve good intraocular levels, and we recommend their use in cases of *Bacillus* endophthalmitis as adjunctive therapy. Intravenous clindamycin is used in treating some systemic *Bacillus* infections, but the intraocular penetration of systemic clindamycin is unknown. Early vitrectomy is an important component of therapy for most cases of *Bacillus* endophthalmitis and other fulminant endophthalmitis cases, as discussed below.

Oral ciprofloxacin has been shown to have adequate intraocular penetrance with 500 mg twice-daily dosing and may be used for cases of suspected *Pseudomonas* infection, including cases in which ceftazidime cannot be used [29]. If the patient is at high risk for fungal infection, intravitreal and systemic voriconazole may be added empirically [61, 79]. Systemic voriconazole is usually given intravenously

for at least the first two doses and then changed to oral administration as it is well absorbed.

In cases of fungal endophthalmitis, intravitreal plus systemic voriconazole is the treatment of choice for most fungi [80, 81]. The usual intravitreal voriconazole dose is 50–100 μg/0.1 mL. Some molds are resistant to voriconazole, and intravitreal amphotericin B at 5–10 μg/0.1 mL can be administered [82]. Vitrectomy should be performed if significant vitritis is present. The treatment of exogenous fungal endophthalmitis is discussed in detail in Chapter 11.

After empiric antibiotic treatment, most patients will improve clinically by the time culture results return. Patients may then receive therapy tailored to the specific microbe grown on culture, unless cultures are negative, in which case the ophthalmologist should continue empiric therapy if the patient is improving. If no improvement is seen after 48–72 h of intravitreal antibiotic therapy in culture-negative cases, it is recommended to repeat imaging and examination to rule out occult IOFB and to consider other microbiological etiologies of endophthalmitis, such as fungal or polymicrobial. Polymicrobial infections are generally more severe and should receive combination therapy [23, 83].

During the course of intravitreal antibiotic therapy, significant intraocular inflammation can occur due to a combination of bacterial endotoxin release and host factors, resulting in membrane formation and tractional retinal detachment [84]. To prevent exacerbation of anatomical and functional damage, steroids may be used after observing clinical improvement following administration of intravitreal injections, but the efficacy of steroids is controversial. Intravitreal injections may variably alter the efficacy of antibiotics and antifungals in eyes with endophthalmitis [34, 85–87], and whether it actually decreases inflammation in the infected eye may differ based on timing and microbiological spectrum [88]. We generally use topical steroids, such as prednisolone acetate 1 % drops 4 times a day, instead of intravitreal or systemic administration, due to the lack of definitive data on its safety and efficacy in patients with endophthalmitis [34].

It is important to note that the intravitreal dose of antibiotic after gas or silicone oil tamponade must be adjusted accordingly, as discussed in the next section.

### *9.4.2 Surgical*

In cases of fulminant endophthalmitis, an urgent PPV is recommended to decrease microbial and toxin load [53]. An undiluted vitreous sample should be sent for culture and staining, and the highly diluted vitreous fluid from the vitrectomy machine cassette also has been reported to be sensitive for culture-positive cases of endophthalmitis [89]. A core vitrectomy with preservation of the posterior hyaloid is generally employed to prevent occult breaks in the friable retina. The procedure can be repeated if necessary, typically 1 week after the initial vitrectomy, once the intravitreal antibiotics have had time to act. Silicone oil tamponade may be used as prophylaxis in cases with a high suspicion of

retinal tears [90]. In a prospective randomized controlled study of post-traumatic endophthalmitis cases conducted by Azad et al. in 2003, complete vitrectomy with silicone oil tamponade resulted in fewer retinal detachments postoperatively and better visual outcome compared with core vitrectomy alone. Due to the poor view of the retinal details during vitrectomy in such severely infected cases, small iatrogenic retinal holes and tears may go undiagnosed intraoperatively, and prophylactic use of silicone oil may help in tamponading these untreated holes.

Intravitreal broad-spectrum antibiotics, vancomycin 1 mg/0.1 mL and ceftazidime 2.25 mg/0.1 mL, are used at the end of the case. If a gas or silicone oil tamponade is needed, the intravitreal antibiotic dosage should be decreased by half [91, 92]. Vancomycin has then been added to the irrigating solution during the vitrectomy in some centers [34].

## 9.5 Outcome

### *9.5.1 Functional*

Early infection in traumatic eyes is difficult to diagnose since the signs and symptoms of infection may overlap that of expected post-traumatic ocular finings. Even if the treatment for endophthalmitis is expedited and the infection resolves quickly, functional outcome may be limited by the inherent nature of the injury.

**Table 9.3** Ocular trauma score

| | | Raw points |
|---|---|---|
| Initial visual acuity | NLP | 60 |
| | LP-HM | 70 |
| | 1/200–19/200 | 80 |
| | 20/200–20/50 | 90 |
| | 20/40 or better | 100 |
| Globe rupture | | −23 |
| Endophthalmitis | | −17 |
| Perforating injury | | −14 |
| Retinal detachment | | −11 |
| Afferent pupillary defect | | −10 |

As developed by Kuhn et al. [93]. The raw score was then compared against an evidence-based table of scores correlating with final visual acuity
*NLP* no light perception, *LP* light perception, *HM* hand motion

The ocular trauma score (OTS, Table 9.3) ranges from 0 to 100 and was developed to predict final visual acuity (VA) in eyes that sustained trauma [93]. It has proven to be an effective gauge of visual prognosis, with a score of 100 conferring the best outcome. Endophthalmitis, if present with OGI, lowers the score by 17 points. Final visual acuity 20/40 or better was seen in less than half of post-traumatic cases in the prospective 2013 multicenter French Institutional Endophthalmitis Study (FRIENDS) in which all 17 cases were treated with the same intravitreal regimen of vancomycin and ceftazidime [64].

This scoring system has been shown to offer prognostic value in pediatric patients as well, regardless of patient compliance in afferent pupillary defect assessment [94].

Delayed treatment >72 h after onset of endophthalmitis may portend worse visual prognosis as demonstrated in Nicoara et al.'s study from Romania of 14 eyes with post-traumatic endophthalmitis [44], while protective factors may include initial VA better than LP, infection with *Staphylococcus epidermidis*, and culture-negative cases, which also was shown in the prospective FRIENDS study. Initial VA and culture results (culture-negative versus positive) were not shown to have a significant effect on final VA in the Romanian study, while culture-negative cases were associated with a better visual prognosis in a case series from India of 97 eyes with post-traumatic endophthalmitis [95]. Concurrent retinal detachment is independently associated with a lower final VA, as demonstrated by both the FRIENDS group and the Romanian case series.

### *9.5.2 Enucleation*

In severely infected blind, painful eyes in which the infection is fulminant and not responding to antibiotic therapy, enucleation may be considered as a therapeutic option. Occasionally, an open globe may present with panophthalmitis. Systemic antibiotics should be started promptly, and every attempt should be made to close the eye before intravitreal antibiotics are used. However, such eyes are extremely difficult to rehabilitate. If it is not feasible to repair the open globe, primary enucleation may be the only therapeutic option. It is controversial whether eyes with endophthalmitis post-OGI have a higher incidence of enucleation than OGI eyes without endophthalmitis [26, 32, 96].

Primary implant placement has been recommended in recent years with either porous or nonporous implants, due to a minimal chance of implant extrusion [97]. However, implants are not commonly used during enucleations of eyes with active infection [98]. Based on the degree of purulence, microbiological spectrum, and inflammation in the affected eye, concurrent implant placement during the enucleation procedure in patients with endophthalmitis following trauma should be evaluated on an individual basis.

**Table 9.4** Prophylactic antibiotic therapy following eye trauma depending on type of injury and presence of risk factors (Table 9.2); protocol used at Rutgers New Jersey Medical School. Other regimens have been described in the literature (see text)

| Condition | Prophylactic antibiotics |
|---|---|
| Globe rupture | IV fluoroquinolone × 1–3 days<br>Oral levofloxacin or ciprofloxacin × 7 days |
| 1+ risk factors | IV vancomycin 1 g/12 h + ceftazidime 1 g/8 h × 3 days<br>Oral levofloxacin or ciprofloxacin × 7 days<br>(Intravitreal vancomycin 1 mg/0.1 mL + ceftazidime 2.25 mg/0.1 mL: if multiple risk factors) |

Can also be used as empiric treatment while awaiting culture sensitivities

*IV* intravenous

## 9.6 Prophylaxis

Immediate antibiotic prophylaxis should be started in cases of OGI, given that an open wound can provide organisms with direct access into the eye to cause infection. Prophylactic therapy may involve use of fluoroquinolones for broad-spectrum gram-positive and gram-negative coverage; vancomycin for gram-positive coverage, including strains resistant to beta-lactams; and ceftazidime, a fourth-generation cephalosporin, for gram-negative coverage that includes *Pseudomonas.*

For OGIs treated at the Institute of Ophthalmology and Visual Science (Rutgers New Jersey Medical School), we use a 1- to 3-day course of intravenous fluoroquinolone followed by a 7-day course of oral levofloxacin or ciprofloxacin as prophylaxis against post-traumatic endophthalmitis. In the presence of one or more risk factors for endophthalmitis (Table 9.2), at least 3 days of intravenous vancomycin 1 g every 12 h and ceftazidime 1 g every 8 h is suggested, followed by 7 days of oral levofloxacin or ciprofloxacin upon discharge [34]. At other centers, 48 h of prophylactic intravenous vancomycin plus ceftazidime is administered (no follow-up oral therapy) for all OGIs, with a resulting post-traumatic endophthalmitis rate of 0.9 % [24].

Prophylactic intravitreal antibiotic injection has been effective in high-risk cases. A prospective 2003 study by Narang et al. demonstrated that prophylactic intravitreal 1 mg/0.1 mL vancomycin and 2.25 mg/0.1 mL ceftazidime injections in patients with OGI led to a significant decrease in cases of endophthalmitis [29]. Soheilian et al. published a prospective randomized trial of intravitreal antibiotic prophylaxis, reporting that intravitreal injection of 40 μg/0.1 mL of gentamicin sulfate and 45 μg/0.1 mL of clindamycin (in addition to 5 days of postoperative intravenous antibiotics) was associated with a significantly lower risk of endophthalmitis, but only in eyes with an IOFB [45]. However, intravitreal vancomycin plus ceftazidime would be preferred to clindamycin and gentamicin in most centers due to the potential retinal toxicity of gentamicin and the increasing resistance of staphylococci and streptococci to clindamycin. We recommend intravitreal vancomycin 1 mg/0.1 mL plus ceftazidime 2.25 mg/0.1 mL, in addition to systemic antibiotics, if multiple risk factors are pres-

ent, especially if an IOFB is present (Table 9.4). In patients allergic to penicillin, amikacin 200–400 μg/0.1 mL may be considered as a substitute for ceftazidime.

## 9.7 Summary

- *Trauma* is a leading cause of endophthalmitis, comprising one-fifth to one-third of cases.
- The most common causes of infectious post-traumatic endophthalmitis are *coagulase-negative staphylococci and Bacillus* in adults and *Streptococcus* in children. Patients with *Bacillus* infections may present with *fulminant* signs and symptoms, including *corneal ring ulcer* on exam.
- The risk of endophthalmitis after OGI is increased in cases with *delayed* OGI management, trauma in a *rural* area, *lacerated* globe*, dirty wound*, *intraocular foreign body*, and *lens capsule disruption*.
- Antibiotic prophylaxis involving IV antibiotics is recommended: effective regimens appear to include *quinolones* alone or IV *vancomycin plus ceftazidime*.
- If endophthalmitis is clinically suspected, *samples* of aqueous and/or vitreous should be urgently obtained and empiric *intravitreal* antibiotics injected. *Systemic* antibiotics are usually also started. Treatment can then be tailored based on culture or PCR results and sensitivities.
- Surgical management generally involves *intravitreal* antibiotics with or without *vitrectomy*. If patients do not respond within 24–48 h to initial treatment with intravitreal antibiotics alone or if they worsen after intravitreal antibiotic injection, then vitrectomy should be done combined with *re-injection* of intravitreal antibiotics.
- *Delayed treatment* and the presence of *retinal detachment* can lead to a poorer visual outcome.
- Blind eyes with fulminant infection may need *enucleation*; risks and benefits of implant placement must be assessed on an individual basis.
- Eyes with endophthalmitis generally have an extremely *guarded* visual prognosis; diligent aggressive medical and surgical management is needed to attain maximal possible visual outcome.

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# Chapter 10
# Endogenous Endophthalmitis

**Avni V. Patel and Lucy H. Young**

## 10.1 Introduction

Endogenous endophthalmitis results when there is ocular seeding from a bloodstream infection. Endogenous endophthalmitis is most frequently encountered in patients who are diabetic, chronically immunocompromised (e.g., on chemotherapeutic agents or transplant recipients), and abuse illicit intravenous drugs or who have chronic indwelling central venous catheters. Other risk factors include endocarditis, urinary tract infections, liver abscess, recent surgery, and hepatobiliary or gastrointestinal procedures [2, 12, 35, 39]. While endogenous endophthalmitis is less often encountered in patients without these risk factors, procedures causing transient bacteremia or fungemia may predispose otherwise healthy patients. Cases of endogenous endophthalmitis have been reported in patients after colonoscopy, acupuncture, dental procedure, or even in the peripartum period [26, 40, 55, 57, 58].

The diagnosis of endogenous endophthalmitis is suspected when there are clinical findings consistent with endophthalmitis supported by positive blood cultures consistent with either bacteremia or fungemia. Endogenous endophthalmitis occurs in a higher proportion of patients with fungemia than patients with bacteremia [10, 38, 52]. The relative proportion of fungal versus bacterial cases varies by geographic location. In Western countries and Australia, fungi account for up to two-thirds of cases [46, 59], while in East Asian countries such as Korea and Taiwan, bacterial pathogens

A.V. Patel, MD
Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear, Boston, MA, USA

L.H. Young, MD, PhD (✉)
Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA
e-mail: Lucy_Young@meei.harvard.edu



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predominate [29]. The leading bacterial pathogens responsible for endogenous endophthalmitis are gram-positive cocci such as *Staphylococcus aureus* and streptococci in Western countries and gram-negative bacilli, primarily *Klebsiella pneumoniae*, in many Asian countries [2, 27, 46, 54]. *Candida* is the most common fungal species causing endogenous endophthalmitis, followed by *Aspergillus* [30, 50].

Patients presenting with endogenous endophthalmitis may have systemic symptoms such as evidence of sepsis and symptoms such as fevers, chills, and malaise. However, a significant proportion of patients may present with ocular symptoms alone [35]. Nearly 20 % of cases in one series had no systemic symptoms at the time of presentation [20], and in two series, over 50 % of cases presented first to ophthalmologists [20, 35]. This underscores the importance of the healthcare practitioner maintaining a heightened suspicion for the disease even in those without overt predisposing conditions and eliciting a thorough history of potential risk factors. There is a high rate of ocular as well as systemic morbidity associated with endogenous endophthalmitis, making prompt diagnosis essential for useful vision to be preserved. Given this, ophthalmologists, infectious disease specialists, and general practitioners must be aware of this disease and its management.

## 10.2 Endogenous Bacterial Endophthalmitis

### *10.2.1 Pathogenesis and Epidemiology*

Endogenous bacterial endophthalmitis occurs when bacteria cross the blood-ocular barrier from the bloodstream to infect the eye. The pathogenesis is discussed in detail in Chap. 2. Endogenous bacterial endophthalmitis is rare, accounting for only 2–6 % of the total cases of endophthalmitis [23, 49, 51].

While there is a moderate incidence of minor retinal lesions such as hemorrhages, Roth spots, or cotton wool spots in patients with bacteremia (6–26 %), an exceedingly small number of patients with bacteremia will develop endophthalmitis [3, 33]. In a study of 202 patients with bacteremia, 12 patients had retinal lesions consisting of microhemorrhages and cotton wool spots, but no patients developed endophthalmitis [3]. Similarly, in a study of 101 patients with bacteremia, 24 patients had minor retinal lesions, but only one developed endogenous endophthalmitis [33].

Most patients who present with endogenous endophthalmitis have risk factors for systemic disease, such as diabetes, malignancy, renal failure, or cirrhosis, predisposing them to endogenous infection [34]. The most common sources of bacteremia include endocarditis, urinary tract infections, abdominal abscesses, soft tissue infections, pneumonia, indwelling central venous catheters, invasive procedures or endoscopy which may cause transient bacteremia, and intravenous drug abuse. In a series from the U.S., endocarditis was the most common source of endogenous bacterial endophthalmitis, causing nearly 40 % of cases [35]. Translocation of bacteria from the gastrointestinal tract or urinary tract was the second most common cause. In contrast, endocarditis was the source of infection in only 14 % of cases in a series

from Japan [34] and in none of the cases in a series from Hong Kong [56]. The most common pathogens causing endogenous bacterial endophthalmitis in the U.S. and Western countries include *Staphylococcus aureus* (25 %); *Streptococcus* species (32 %), including *S. pneumoniae*, *S. milleri*, and group A and B streptococci; and gram-negative bacilli (30 %), including *Escherichia coli* [35] (Jackson et al.). In East Asian countries such as Taiwan and Singapore, *Klebsiella pneumoniae* is the most common cause of endogenous bacterial endophthalmitis and is often associated with liver abscesses [54].

### *10.2.2 Ocular Manifestations*

Classic ocular symptoms of endogenous bacterial endophthalmitis include pain, blurred vision, and redness. In one study, two-thirds of patients had ocular pain on presentation [20]. Signs on ophthalmic examination include anterior chamber inflammation, hypopyon or fibrin in the anterior chamber, elevated intraocular pressure, corneal edema, and retinal hemorrhages and infiltrates. Bilateral involvement is seen in 12–29 % of cases, although one eye may be worse than the other [14, 20, 34, 35].

Endophthalmitis is often a harbinger of serious systemic infections. Patients may present with symptoms of eye pain and blurred vision prior to systemic manifestations of their underlying infection. Greater than 50 % of patients in one series saw an ophthalmologist initially [35]. Another series showed less than 20 % of patients had fever on initial presentation of endogenous endophthalmitis [2].

This frequent absence of systemic symptoms leads to a high incidence of misdiagnosis in cases of endogenous bacterial endophthalmitis. In one study of endogenous bacterial endophthalmitis patients, there was a delay in diagnosis in 29 % of patients [35]. Other studies similarly show an incorrect diagnosis occurs in these patients at a rate of 16–22 % [14, 20]. The diagnosis for which endogenous bacterial endophthalmitis is most commonly initially confused in adults is non-infectious uveitis, which accounted for 38 % of initial diagnostic errors in one review of the literature [20]. Conjunctivitis, acute glaucoma, and endogenous fungal endophthalmitis were the other most common initial diagnostic errors found in this study, the last primarily because endogenous bacterial endophthalmitis may be initially misdiagnosed as endogenous fungal endophthalmitis in intravenous drug users since fungal infection is more common in this population [20].

### *10.2.3 Diagnostics*

Blood cultures, at least two sets, should be obtained in all patients in whom endogenous endophthalmitis is being considered, even in patients who are afebrile. The gold standard for the diagnosis of endogenous endophthalmitis is obtaining

intraocular fluid for culture. An anterior chamber tap and vitreous sampling by fine needle aspiration or vitrectomy are the ways to obtain an intraocular sample. Cultures of vitreous are more sensitive for detecting the pathogen than cultures of aqueous [22, 2], and vitreous samples obtained by vitrectomy have a higher yield than vitreous aspirate samples. The best information about the sensitivity of various intraocular samples comes from large studies of exogenous endophthalmitis. In the Endophthalmitis Vitrectomy Study, a study of 420 post-cataract surgery endophthalmitis cases, vitreous samples obtained by vitrectomy were more likely to be culture positive (90 %) than vitreous samples obtained by aspirate/biopsy (75 %) or aqueous samples (14 %) [42]. A series of 206 patients with endophthalmitis demonstrated that vitreous sampling by vitrectomy was more likely to be positive (76 % vs. 43 %) than fine needle vitreous aspiration, though not all patients had an endogenous source [10].

The aqueous or vitreous specimen should be sent for Gram stain as well as aerobic, anaerobic, and fungal cultures. Should there be any extraocular fluid collections or manifestations of infection such as abscess, a specimen should also be sent from this site. Polymerase chain reaction (PCR) is increasingly being used in the diagnosis of endophthalmitis as it greatly amplifies the quantity of bacterial DNA available for analysis and increases the chances of detecting even a single organism [36]. The details of PCR and its role in the diagnosis of endophthalmitis are discussed in Chap. 4.

Patients with endogenous endophthalmitis should additionally have a systemic evaluation to localize a primary source of infection. This must include blood cultures and urine culture, a chest x-ray to look for pneumonia, and usually an echocardiogram to rule out endocarditis. Abdominal imaging, such as computed tomography (CT) scanning, may be indicated, particularly in patients with *Klebsiella pneumoniae* infection, and additional testing should be done based on patient symptoms (e.g., imaging of the spine in patients with back pain). Blood cultures are more likely to be positive than vitreous culture in endogenous bacterial endophthalmitis. In several studies, almost 75 % of cases of endogenous bacterial endophthalmitis demonstrated blood culture positivity [20, 35, 54]. Blood cultures may be falsely negative if intravenous antibiotics are started before they are obtained.

### *10.2.4 Management*

Systemic antibiotics are essential in the treatment of patients with endogenous bacterial endophthalmitis, in order to treat the extraocular focus of bacteremia. The duration of treatment with systemic antibiotics is based upon the underlying source of bacteremia; for cases of endocarditis, for example, a 6-week course is usually recommended.

Systemic antibiotics alone are inadequate to treat bacterial endophthalmitis, and injection of intravitreal antibiotics should be performed as soon as possible. One

analysis suggests that eyes that received intravitreal antibiotics in addition to systemic treatment were less likely to require evisceration or enucleation [20]. In general, vitreous sampling by needle aspirate or vitrectomy, with concomitant intravitreal antibiotics, is the current standard of care. In the four largest series of endogenous bacterial endophthalmitis, 82 % underwent vitreous biopsy and 81 % received intravitreal antibiotics [8, 28, 35, 54].

The most commonly used intravitreal antibiotics in cases of endogenous bacterial endophthalmitis are vancomycin and ceftazidime. Intravitreal vancomycin 1 mg is most commonly given for gram-positive infection. Gentamicin has fallen out of favor due to the risk of retinal vascular toxicity leading to macular infarction [1]. For gram-negative infection, ceftazidime has been shown to be safe and is given as a dose of 2 or 2.25 mg [6]. Alternatively, amikacin may be used for gram-negative infections, particularly in those patients allergic to ceftazidime or for ceftazidime-resistant gram-negative infections. There have been case reports of macular infarction after the use of intravitreal amikacin [13], although the incidence is thought to be less than after gentamicin. Amikacin is given as a dose of 0.4 mg. All of the intravitreal antibiotics listed here are diluted in 0.1 ml sterile water or saline.

In addition to blood cultures and intravenous antibiotics, we recommend vitreous biopsy by either needle aspirate or vitrectomy, plus the injection of intravitreal antibiotics. Vitrectomy should be considered in eyes with severe vision loss (light perception or worse) or in those with diffuse or fulminant vitreous involvement, and it should also be considered for cases without significant improvement after 24–48 h of antibiotics. A second injection of intravitreal antibiotics may be recommended in cases where there is no improvement after 48 h. Vancomycin and/or ceftazidime may be given based upon culture results as a second injection; however, amikacin should be avoided due to the risk of retinal toxicity unless the infection is due to ceftazidime-resistant gram-negative bacteria.

### *10.2.5 Prognosis*

The prognosis for patients with endogenous bacterial endophthalmitis is poor; however, with appropriate and timely management, patients may retain useful vision. A review of endogenous bacterial endophthalmitis cases reported in the literature between 1986 and 2001 found that the final visual acuity was count fingers or better in 32 %, hand motion or light perception in 12 %, no light perception in 24 %, and phthisis, evisceration, or enucleation in 33 % [20]. Similar results were found in a study of East Asian patients with 34 % of patients retaining count fingers or better final vision and 16 % of eyes were eviscerated or enucleated [54]. Those patients presenting with bacterial panophthalmitis were more likely to require evisceration or enucleation due to the severity of infection, according to several studies [14, 46]. Vitrectomy may aid in decreasing the burden of infectious organisms. Studies suggest that eyes that undergo vitrectomy are nearly three times as likely to retain

useful vision and less likely to require evisceration or enucleation [20]. Several other factors have been associated with a poorer prognosis, including a delay in diagnosis, infection with a more virulent organism, the use of inappropriate antibiotics, and infection by gram-negative organisms [5, 14, 54]. Additionally, there is significant mortality associated with the systemic infection and extraocular manifestation of the infection. Studies have found varying rates of mortality from 5 to 32 % in patients with endogenous bacterial endophthalmitis given the gravity of the systemic infection [3, 20]. This is not surprising given most patients are seriously ill and debilitated and often have severe and disseminated infection.

## 10.3 Endogenous Fungal Endophthalmitis

### *10.3.1 Endogenous* Candida *Endophthalmitis*

*Candida* is the most common fungal cause of endogenous endophthalmitis. Most cases of *Candida* endophthalmitis occur endogenously through hematogenous spread from the bloodstream to the highly vascular choroid [53]. Risk factors for *Candida* endophthalmitis in hospitalized patients include indwelling central venous catheters, total parenteral nutrition, neutropenia, recent gastrointestinal surgery, broad-spectrum antibiotic use, and glucocorticoid therapy [11, 17]. In outpatients who do not have a history of recent hospitalization or a recent indwelling central venous catheter, the major risk factor is intravenous drug abuse. In a study from Australia, 70 % of patients presenting with endogenous fungal endophthalmitis were intravenous drug users [9]. *Candida* endogenous endophthalmitis occurs with a highly variable rate and has been reported in anywhere from 0 to 78 % of patients with candidemia [4, 10, 38, 47]. The incidence of chorioretinitis is much higher than endophthalmitis with vitritis; a large prospective trial of candidemic patients reported 11 % with ocular involvement but only 1.6 % with significant vitritis [37].

### *10.3.2 Ocular Manifestations of* Candida *Endophthalmitis*

As *Candida* initially spreads to the choroid, fungal endophthalmitis usually manifests initially as a focal choroiditis or chorioretinitis [30, 50]. The infiltrates develop into white, fluffy lesions extending into the vitreous, often classically presenting as a “string of pearls” or snowballs. It is at this point that affected patients may first develop symptoms of floaters and decreased vision. Retinal vascular sheathing and multiple satellite lesions may be seen (Fig. 10.1). Endogenous endophthalmitis with yeast usually presents more gradually and with better visual acuities than that due to bacteria [50].

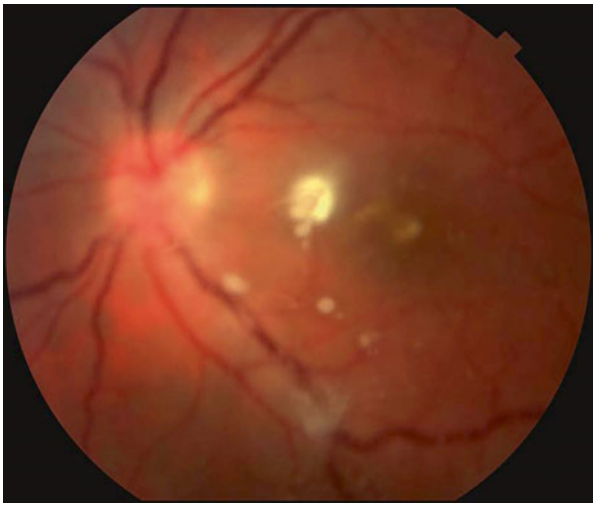

**Fig. 10.1** A 23-year-old healthy man presented with increasing floaters and blurry vision for 2 weeks as well as increasing redness and pain in the left eye for two days. He was found to have endogenous *Candida* endophthalmitis, and a history of intravenous drug use was elicited

### *10.3.3* Aspergillus *and Other Types of Endogenous Mold Endophthalmitis*

*Aspergillus* is the second most common cause of fungal endogenous endophthalmitis. There are more than 200 species of *Aspergillus* (approximately 16 occur as human pathogens); however, the most common ocular pathogen is *Aspergillus fumigatus*. Reported risk factors for disseminated aspergillosis include chronic pulmonary disease and chronic immunosuppression, particularly after liver transplantation or treatment with systemic corticosteroids [19, 31, 53]. Ridell et al. reported in a review of 86 cases published in the literature 1949–2001 that 43 % of patients with endogenous *Aspergillus* endophthalmitis had received treatment with corticosteroids, 27 % had a history of intravenous drug abuse, 23 % were solid organ transplant recipients, and 17 % were patients with chronic lung disease [43]. Although *A. fumigatus* was the most common species, *A. flavus* was also common and was associated with intravenous drug abuse. Similar to other endogenous infections, *Aspergillus* organisms seed the eye via hematogenous spread to the choroid [30].

Other molds may cause endogenous endophthalmitis. In a study from a Texas cancer center, all 15 patients with endogenous mold endophthalmitis had hematologic malignancies and half had undergone bone marrow transplantation [25]. The molds isolated were *Fusarium* (33 %), *Aspergillus* (27 %), *Scedosporium* (27 %), and *Mucor* and *Rhizomucor* (13 %).

### *10.3.4 Ocular Manifestations of* Aspergillus *Endophthalmitis*

The central macula or posterior pole is often involved in endogenous *Aspergillus* infection. *Aspergillus* endophthalmitis classically presents with a central, confluent, yellowish macular infiltrate beginning in the choroid and subretinal space [53]. The degree of retinal inflammation may vary, with cases progressing from a subretinal or subhyaloid infiltrate to full-thickness retinal involvement with hemorrhages [41]. Retinal vascular occlusion, choroidal vascular occlusion, and exudative retinal detachment may be associated with *Aspergillus* endophthalmitis and when present account for poorer visual outcomes compared to *Candida* infections [21].

### *10.3.5 Diagnostic Considerations for Endogenous Fungal Endophthalmitis*

Just as in suspected endogenous bacterial endophthalmitis, blood cultures should be obtained in any patient with possible endogenous fungal endophthalmitis. Negative blood cultures do not exclude fungal endophthalmitis, as fungemia may have been transient. This is particularly true in patients with intravenous drug abuse, who frequently have no systemic symptoms when they present with endogenous fungal endophthalmitis. Hospitalized patients with endogenous fungal endophthalmitis, on the other hand, are usually quite ill, but even they may have falsely negative blood cultures. Depending on the type of fungus causing the infection and the clinical setting, an echocardiogram and CT scans of the lungs and abdomen may be indicated. Even in patients who are immunocompromised or have evidence of disseminated infection, the yield of blood cultures is low in fungal endophthalmitis compared to bacterial cases [53]. A vitreous aspirate by fine needle biopsy or vitrectomy is recommended as with cases of bacterial endophthalmitis. While this is the gold standard for the diagnosis of fungal endophthalmitis, the rates of positive cultures from vitreous sampling vary from 40 to 92 % [7, 19, 30, 41, 50]. The yield of positive cultures from vitrectomy is higher than from vitreous aspirate. A study of endogenous fungal endophthalmitis reported a 92 % positive culture rate in the eyes that underwent primary vitrectomy versus only 44 % in eyes that had a primary vitreous aspirate [30].

Once a sample has been obtained, organisms can be sent for special stains and cultures. Under direct microscopy of Gram-stained smears, *Candida* appears as budding yeast or pseudohyphae, but molds are almost never seen. Potassium hydroxide (KOH) dissolves human cells, and calcofluor white, the preferred stain, stains the cell wall of the fungi causing them to fluoresce. *Candida* will typically grow on routine blood agar, but it is important to request fungal cultures in any case in which a yeast or mold is suspected. Sabouraud agar is used for fungal cultures, and incubation is at a lower temperature for fungal cultures than bacterial cultures. Polymerase chain reaction testing of intraocular fluids may be useful in some cases;

this is discussed further in Chap. 4. A study of four patients with *Candida albicans* endophthalmitis, two of whom had negative vitreous cultures, found positive results of polymerase chain reaction studies for *Candida albicans* in all four cases [18].

### *10.3.6 Treatment of Endogenous Fungal Endophthalmitis*

All patients with endogenous fungal endophthalmitis should receive systemic treatment with antifungal medications. Sources of fungal infection, if any, should be identified and treated. If an indwelling central venous catheter is the source of *Candida* endophthalmitis, for example, that indwelling line should be removed. In addition to systemic antifungal antibiotics, patients with endogenous *Candida* endophthalmitis with vitritis and those with endogenous mold endophthalmitis should also receive intravitreal amphotericin B or voriconazole (for voriconazole-susceptible fungi). Vitrectomy is an important component of treatment in some cases of endogenous fungal endophthalmitis, particularly in mold endophthalmitis, as discussed below. The duration of systemic therapy will be determined primarily by the underlying systemic fungal infection, but typically treatment is given for 4–6 weeks [43]. Immunocompromised patients with systemic mold infections are often treated with even longer courses of antifungal therapy (e.g., months).

**Antifungal Agents** Amphotericin B, previously used widely in the treatment of fungal endophthalmitis, is less favored than azole antibiotics for azole-susceptible fungi, due to the better intraocular penetration and lower systemic toxicity of the azoles. Systemic liposomal amphotericin is now preferred to amphotericin when systemic amphotericin is indicated; amphotericin has limited intraocular penetration and significant nephrotoxicity. Liposomal amphotericin appears to achieve higher concentration than amphotericin in the rabbit eye in experimental studies [15]. Flucytosine, which achieves good intraocular levels, is sometimes used in combination with amphotericin for treating *Candida* infections, although flucytosine may have bone marrow toxicity. Note that flucytosine has no activity against *Candida krusei*, a particularly resistant species of *Candida*.

Azoles are now preferred for the treatment of fungal endophthalmitis for azole-susceptible strains. Triazoles, such as fluconazole and voriconazole, provide greater than 90 % oral bioavailability and excellent intraocular penetration from the systemic circulation [43, 45]. Fluconazole has activity against most *Candida* isolates (*C. krusei* and some *C. glabrata* strains are exceptions), but not against molds and should not be used to treat systemic mold infections or mold endophthalmitis. *Candida* isolates should be tested for fluconazole sensitivity. Fluconazole is given as a 12 mg/kg loading dose followed by a 6–12 mg/kg daily dose (usually 400–800 mg daily orally). Voriconazole is given as 6 mg/kg every 12 h for two doses, followed by 4 mg/kg twice daily; the intravenous form is usually given for initial doses. Dosing of fluconazole and voriconazole should be reduced for renal

dysfunction, and the prescribing physician should also check for potential drug-drug interactions with the patient's other medications. Voriconazole has excellent activity against nearly all strains of *Candida*, including fluconazole-resistant strains, as well as most molds, including *Aspergillus* and *Fusarium*. Voriconazole is the treatment of choice for systemic *Aspergillus* infections and therefore also the treatment of choice for endogenous *Aspergillus* endophthalmitis. Trough levels of voriconazole should be monitored approximately 1 week after starting therapy to ensure that adequate levels have been achieved. Liver function tests and other labs should be monitored periodically with any azole treatment. Itraconazole has poor penetration into the vitreous and is not recommended for treating fungal endophthalmitis. There is little information about vitreous penetration of posaconazole or its use in endogenous fungal endophthalmitis.

Echinocandins have excellent activity against *Candida* species, including fluconazole-resistant species, but these agents do not achieve adequate vitreous concentrations, so these cannot be recommended for treating *Candida* endophthalmitis.

**Endogenous *Candida* Endophthalmitis** Early *Candida* chorioretinitis may respond to systemic therapy alone, but close follow-up is necessary as some cases progress to vitritis despite therapy. Fluconazole is the treatment of choice for fluconazole-susceptible strains; voriconazole or liposomal amphotericin is used to treat fluconazole-resistant strains (e.g., *C. krusei* and some strains of *C. glabrata*). For cases of *Candida* endophthalmitis with vitritis, we recommend intravitreal injection of antifungals in addition to systemic treatment, particularly in cases with macular involvement or macula-threatening lesions. Either amphotericin (5 or 10 μg/0.1 mL of sterile water) or voriconazole (100 μg/0.1 mL of sterile water) can be given as an intravitreal injection. Patients with *Candida* endophthalmitis with moderate to marked vitritis usually benefit from vitrectomy, if they are surgical candidates. Some studies have shown that early rather than delayed vitrectomy is particularly important in such patients. In a study of 12 patients with injection drug abuse and *Candida albicans* endophthalmitis with severe vitritis, the seven patients who had an early vitrectomy (≤1 week) had a good visual outcome, while four of the five patients in whom vitrectomy was delayed or not performed had a very poor visual outcome [32]. In another study involving 44 eyes with endogenous *Candida* endophthalmitis, eyes that underwent early vitrectomy (≤1 week) had a lower rate of retinal detachment than eyes with delayed vitrectomy, 8 % versus 41 %, respectively [44].

**Endogenous Mold Endophthalmitis** Endogenous mold endophthalmitis is more difficult to treat than endogenous *Candida* endophthalmitis. Systemic antifungal therapy is indicated in all cases, and the choice of agent should be based on the optimal antibiotic needed to treat the systemic mold infection. Fluconazole has no activity against molds and should not be used. Itraconazole does not penetrate the vitreous and should not be used. Voriconazole achieves excellent levels in the vitreous, approximately 40 % of serum levels with oral administration [16], and is active against *Aspergillus* and most strains of *Fusarium*. Liposomal amphotericin is typi-

cally used for voriconazole-resistant fungi. In addition to systemic antifungal therapy, an intravitreal antifungal injection should be performed; intravitreal amphotericin or voriconazole may be used depending on the susceptibility of the mold [24]. One or more repeat injections may be necessary depending on clinical response, with several days interval between injections. In nearly all patients with endogenous mold endophthalmitis who are surgical candidates, vitrectomy should be performed. An intravitreal injection of amphotericin or voriconazole is given at the end of the case. If the infection extends to the anterior segment and a foreign body such as an intraocular lens is present, the foreign body should be removed if possible at the time of vitrectomy.

### *10.3.7 Prognosis for Patients with Fungal Endogenous Endophthalmitis*

Patients with endogenous endophthalmitis caused by *Aspergillus* have worse visual outcomes compared with those caused by *Candida* species [12, 35, 46]. Shen et al. reported none of the eyes in their series with mold endophthalmitis achieved a visual acuity of 20/200 or better, while 53 % of the cases with *Candida* endophthalmitis achieved 20/200 vision or better [48]. Lingappan et al. reported that over half (56 %) of patients with yeast endophthalmitis had a final visual acuity of 20/200 or better, and 42 % achieved visual acuity of 20/50 or better, while only 33 % of mold endophthalmitis cases achieved 20/200 or better, and only 7 % achieved 20/50 or better [30]. The worse visual prognosis of *Aspergillus* endophthalmitis, despite aggressive treatment, may be partly explained by the frequency of macular involvement. In one study of 12 eyes with endogenous *Aspergillus* endophthalmitis, the three without central macular involvement achieved a final visual acuity of 20/25–20/200, while eight eyes with macular involvement had a poor visual outcome (20/400 or worse) [53]. Factors that have been shown to be associated with severe visual loss in fungal endogenous endophthalmitis are poor visual acuity at presentation, lesions located in posterior pole, and the development of retinal detachment, which has been reported to occur in as many as 29 % of patients [30].

## 10.4 Conclusion

Given the high rate of ocular and systemic morbidity associated with either endogenous bacterial or fungal endophthalmitis, ophthalmologists as well as general internists must maintain a high index of suspicion for this disease. This is particularly important in immunocompromised patients, but even in those without overt risk factors who have a history of a recent procedure, which may have predisposed them to transient bacteremia or fungemia. Eliciting a thorough history of recent

systemic symptoms, procedures, or other risk factors such as intravenous drug use is of utmost importance. It is also important to find and control the underlying extraocular source of infection. The effective management of patients with endogenous endophthalmitis relies on close follow-up to monitor the response to treatment and determine the need for further intervention. Collaboration with infectious disease colleagues is essential to providing thorough, safe, and efficacious treatment.

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# Chapter 11
# Exogenous Fungal Endophthalmitis

**Carol A. Kauffman**

## 11.1 Introduction

Exogenous fungal endophthalmitis occurs when a mold or yeast gains access to the aqueous and/or the vitreous from the outside. This contrasts with endogenous endophthalmitis in which the access to the eye is from the bloodstream. With exogenous fungal infection, the initial event is usually penetrating eye trauma, eye surgery, or fungal keratitis (keratomycosis). Some types of injury (penetrating trauma) and some species of fungus (*Fusarium* species) are more likely to progress to involve the posterior segment of the eye.

Differences in risk factors, clinical manifestations, and treatment for exogenous endophthalmitis caused by *Candida* species and molds will be discussed in this chapter.

## 11.2 Exogenous Endophthalmitis Caused by *Candida* Species

### *11.2.1 Mycology and Epidemiology*

*Candida* species are much less likely than molds to cause exogenous endophthalmitis [1–5]. These organisms are part of the normal microbiome in humans and rarely are inoculated into the eye when compared with environmental molds. In two series from the 1990s and early 2000s, *Candida* species accounted for only 12–15 % of

C.A. Kauffman, MD
Division of Infectious Diseases, Veterans Affairs Ann Arbor Healthcare System,
University of Michigan Medical School, 2215 Fuller Road, Ann Arbor, MI 48105, USA
e-mail: ckauff@umich.edu



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cases of exogenous infection [3, 4]. Other reports of exogenous endophthalmitis from the 1990s found no cases due to *Candida* species [6, 7].

Exogenous infection with *Candida* species develops most often after surgery, including cataract extraction, intraocular lens implantation, and corneal transplantation. Trauma and prior keratitis are much less common inciting events. Narang et al. noted that 5 of 27 cases of fungal endophthalmitis following cataract surgery were due to *Candida* species [8], which is similar to data from other centers [3]. *Candida* endophthalmitis following corneal transplantation is a well-known complication of this procedure [9–12]. In one report, two patients were infected with *C. glabrata* thought to have been transmitted from the corneas of a single donor [10].

The largest outbreak of endophthalmitis due to *C. parapsilosis* was traced back to a widely distributed ophthalmic irrigating solution that was contaminated during the manufacturing process. Thirteen patients developed endophthalmitis after this solution was used during cataract surgery [13, 14]. In another report, *Candida parapsilosis* infection occurred in four patients who had an intraocular lens implant performed by one surgeon in his clinic [15]. In this case, an improperly sterilized device used in the procedure, and not the irrigating fluid, was likely the source.

Cases of trauma-associated *Candida* exogenous endophthalmitis have been traced to penetration of the eye by a metal object or by organic material [4]. Contact lens-related *Candida* keratitis with subsequent endophthalmitis has been reported, although infrequently [5, 16].

All species of *Candida* can cause exogenous endophthalmitis [1, 3, 16]. The species vary, depending on the country and the initiating event. *C. parapsilosis* appears to be more common in the U.S. A series from India show more *C. albicans* and also other species, including *C. glabrata* and *C. guilliermondii* [4, 8].

### *11.2.2 Clinical Manifestations*

The usual symptoms of exogenous *Candida* endophthalmitis are a decrease in visual acuity and eye pain that can be severe or mild. The course tends to be subacute in many patients with postoperative infection; visual acuity decreases over days to weeks after cataract surgery [1, 15, 17]. Especially in elderly patients, the course is indolent, and the diagnosis can be missed for weeks [15, 17]. Because of the subacute nature of the symptoms, many patients are given topical corticosteroids before the diagnosis of fungal infection is made. This likely contributes to increased growth of the organism and poorer outcomes [3, 5]. With acute penetrating trauma, symptoms can be more acute and pain can be severe. Symptoms of infection post keratoplasty can present any time from postoperative day 1 to day 48 [11]. Systemic symptoms and signs are absent in nearly all patients, regardless of the mechanism of introduction of *Candida* into the eye.

Examination of the eye shows the traumatic injury if that was a recent antecedent event. In patients who have *Candida* endophthalmitis secondary to keratitis, the corneal infiltrate may extend full thickness, and there may be an infiltrate in the

aqueous humor [5]. Conjunctival injection and corneal edema may be prominent. In the case of postoperative *Candida* endophthalmitis, the external appearance may be normal aside from evidence of recent surgery. However, anterior chamber involvement will be manifested by white blood cells, sometimes forming a hypopyon and keratic precipitates [3, 4, 14]. In some cases, there may be a thick white material or an apparent fungus ball in the anterior chamber [18]. Vitritis, if present, may appear as a diffuse haze or have regions of greater density, sometimes described as "snowballs" or "string of pearls."

### *11.2.3 Diagnosis*

The gold standard diagnostic test is culture of the organism from the eye [19]. If endophthalmitis began with keratitis, corneal scrapings and an aqueous aspirate should be sent for culture. If posterior segment infection is suspected, an aspirate of the vitreous should be obtained for culture. The sensitivity of cultures for molds by vitreous aspirate is low [1], but *Candida* is more easily cultured than most molds. Some cases, particularly indolent cases of postoperative *Candida* endophthalmitis, may require a vitrectomy to establish a diagnosis.

A tentative diagnosis of *Candida* infection can be made by performing direct smears on material obtained from the cornea, aqueous, or vitreous. Gram stain will reveal gram-positive budding yeast cells, but the organisms are more easily visualized by calcofluor white stain, which causes the cell walls of fungi to fluoresce [19, 20]. Any biopsy material should be sent to pathology with the request to look for fungi; stains used to visualize fungi include methenamine silver and periodic acid-Schiff (PAS). *Candida* species often grow on media used for routine cultures (e.g., blood and chocolate agar), but fungal culture on Sabouraud's dextrose agar should also be requested.

Polymerase chain reaction (PCR) is increasingly used for diagnosis because it has the potential to be more rapid and may be more sensitive than culture techniques for some fungi [19, 21–23]. Pan-fungal and species-specific PCR assays are available in reference laboratories, but none of these assays are standardized, and the sensitivity and specificity are not known. The assay itself is rapid, but availability only in reference laboratories remains a problem for rapid diagnosis.

### *11.2.4 Treatment and Outcome*

The treatment of exogenous *Candida* endophthalmitis is best accomplished by combining intraocular therapy with systemic oral azole therapy. An important first step is to define whether the infection is localized to the anterior chamber or whether posterior chamber involvement is present as well. When vitritis is found, therapy must be more aggressive to cure the infection and preserve sight.

If infection is localized to the anterior chamber, which is common with infection secondary to corneal transplantation or keratitis, intracameral amphotericin B or voriconazole frequently is used [24–29]. The dose of amphotericin B is 5 μg in 0.1 mL sterile water, and the dose of voriconazole is 50 μg in 0.1 mL sterile water or saline. Injection of amphotericin B can cause inflammation and eye pain for a day or two. Voriconazole is less irritating than amphotericin B and is preferred if the isolate is susceptible [27, 29].

The half-life of voriconazole in the aqueous is short after intracameral injection, so that administration of voriconazole eye drops every 1–2 h is also recommended [30, 31]. Voriconazole administered as 1 or 2 % eye drops has been shown to penetrate through the cornea and achieve levels from 0.8 to 3.6 μg/mL in the aqueous humor [32, 33]. It appears that the 2 % solution results in similar levels as the 1 % solution [32]. Amphotericin B eye drops do not penetrate through the cornea as well as voriconazole eye drops and are more irritating, but can be used if the organism is not susceptible to voriconazole [27].

The use of systemic azole therapy will improve chances of clearing the infection. The treatment of choice is fluconazole because of its achievement of high intraocular levels (about 70 % of serum levels), its safety, and its lower cost than all other azoles [34]. The only caveat to the use of fluconazole is that the organism should be tested to be certain that it is susceptible to fluconazole. Most strains of *C. albicans* remain susceptible to fluconazole, but many strains of *C. glabrata,* a less common organism in exogenous endophthalmitis, are fluconazole resistant. The fluconazole dose is 400–800 mg daily; this dose is decreased in patients with renal dysfunction.

An alternative agent is voriconazole, which also achieves excellent intraocular concentrations [34, 35]. It is active against many species of *Candida* although *C. glabrata* is increasingly resistant to both fluconazole and voriconazole [36]. The dose is 400 mg twice daily the first day, followed by 200–300 mg twice daily thereafter. Voriconazole has more drug-drug interactions, more adverse effects, and is more expensive than fluconazole. Monitoring of serum concentrations always should be performed when prescribing voriconazole to avoid toxicity and ensure adequate absorption [37].

If posterior segment involvement is suspected, in addition to oral azole therapy, intravitreal injection of amphotericin B, 5–10 μg in 0.1 mL sterile water, or voriconazole, 100 μg in 0.1 mL sterile water or saline, should be given [34]. With dense vitritis, a vitrectomy may be necessary to decrease the burden of organisms and allow antifungal therapy to more easily clear the infection [1, 8, 38].

In patients in whom the *Candida* infection is related to an infected intraocular lens (IOL), the IOL should be removed if at all possible [17]. Failure to clear the infection after months of antifungal azole therapy has been well documented in cases in which the IOL remained in place [15]. This is especially true of infection due to *C. parapsilosis*, which is more likely than some other *Candida* species to form a biofilm on foreign material.

Outcomes of exogenous *Candida* endophthalmitis are variable and depend on how quickly the diagnosis is made and treatment is begun, the initiating event, and whether posterior segment infection is present. Various small series have reported

that 40–64 % of patients have a poor visual outcome after treatment for exogenous *Candida* endophthalmitis [4, 5].

## 11.3 Exogenous Endophthalmitis Caused by Molds

### *11.3.1 Mycology and Epidemiology*

Molds are responsible for most cases of exogenous endophthalmitis. Introduction of the mold into the eye can occur through penetrating trauma, from posterior extension of fungal keratitis, and secondary to ocular surgery. Exogenous mold endophthalmitis is geographic in that it is uncommon in most of North America and Europe, with the exception of the southernmost areas, but very common in tropical and subtropical countries [1, 3–5, 38–41]. The disease has been described most often by ophthalmologists who practice in India.

A host of molds, both hyaline and dematiaceous (pigmented), have been associated with exogenous endophthalmitis. The most common are the hyaline molds, *Aspergillus* and *Fusarium*. In several reports, 54–81 % of cases were due to *Aspergillus* species [4, 7, 8]. However, others have reported a preponderance of *Fusarium* species, especially when associated with prior keratitis [3, 5]. Other hyaline molds that less commonly have caused endophthalmitis include *Acremonium species, Paecilomyces lilacinus*, and *Scedosporium apiospermum* [1, 3, 4, 7]. Dematiaceous molds that have been implicated in exogenous endophthalmitis include species of the genera *Curvularia*, *Alternaria*, *Exophiala*, *Phialophora*, and *Bipolaris* [1, 4, 6, 7].

The geographic distribution of exogenous mold endophthalmitis reflects that of keratomycosis, and in some reports, fungal keratitis is the main predisposing factor leading to exogenous fungal endophthalmitis [3]. Keratomycosis is often associated with trauma involving plant material, explaining its more frequent occurrence in agricultural workers in developing countries [39]. A 15-year study analyzing the risks of progression of keratitis to endophthalmitis in all patients with a diagnosis of keratitis found that significant risk factors included fungal as opposed to bacterial keratitis as well as the use of topical corticosteroids and corneal perforation [5].

A large international outbreak of *Fusarium* keratitis occurred from June 2005 to June 2006 [42–45]. The outbreak was associated with contact lens use, and patients presented with sight-threatening keratitis that progressed to endophthalmitis in some [43–45]. Multiple different strains of *Fusarium* were implicated in this outbreak. The use of ReNu [registered trademark] with MoistureLoc contact lens cleaning solution was highly significantly associated with these cases [42, 43]. Ultimately, it was discovered that patients themselves, because of poor hygienic techniques, likely contaminated their contact lens cases with a variety of different *Fusarium* species. Importantly, the cleansing solution that should have inhibited fungal growth appeared to have lost its fungicidal activity, perhaps related to storage issues at the manufacturing plant [42, 46]. The outbreak ended promptly when ReNu with MoistureLoc was removed from the market.

In the U.S. and Europe, mold infections following ocular surgery are much less common than those due to *Candida* species and bacteria [41, 47]. Ocular surgery in India and other tropical countries is associated with a higher risk of postoperative endophthalmitis caused by molds than by *Candida* species [3, 4, 6, 8]. The organisms most often encountered are *Aspergillus* species. *Aspergillus fumigatus* has been associated with outbreaks of healthcare-associated post-cataract surgery infection traced back to contamination from construction and/or ventilation systems [48].

Other outbreaks of healthcare-associated exogenous mold endophthalmitis have been ascribed to injection of contaminated products [49, 50]. In Istanbul, nine patients undergoing cataract surgery were infected with *Fusarium solani* when contaminated antibiotic solution was injected into the aqueous humor [49]. In two related outbreaks in the U.S. traced back to a single compounding center, a total of 47 patients suffered sight-threatening endophthalmitis related to intraocular injection of contaminated drugs [50]. In the first outbreak, beginning in October 2011, *Fusarium incarnatum-equiseti*, a rarely isolated species, contaminated brilliant blue dye that was injected during vitrectomy in 21 patients. In the second outbreak, which began in December 2011, 26 patients had intraocular injection of triamcinolone that was contaminated with the dematiaceous mold, *Bipolaris hawaiiensis.* Several of the patients in the second outbreak received injections with a combination of bevacizumab and the contaminated triamcinolone, as prepared by this pharmacy [51].

The final mechanism of development of exogenous mold endophthalmitis is penetrating trauma. Again, *Aspergillus* species are the most common organisms isolated, but many different soil organisms and fungal plant pathogens have been implicated [1, 4, 7]. Trauma is from environmental material, such as wood splinters, wire or pieces of metal, and plant material.

### *11.3.2 Clinical Manifestations*

Symptoms vary with the underlying insult that led to the development of exogenous mold endophthalmitis and with the mold involved. Most prominent, of course, is decreased visual acuity, which can range from a minimal decrease from baseline to light perception only. Eye pain is often significant but initially may be mild in some patients, particularly those with indolent infection. Among patients whose infection followed cataract surgery, the course has been described as acute, occurring within days of the procedure, or subacute, with symptoms delayed for weeks to months [3, 4, 8]. The course usually is less indolent than noted with *Candida* infections [4, 8], but some molds that are not usually pathogenic can cause very indolent infections [3].

Among patients who received contaminated intraocular injections, visual loss began several weeks after the injection, but the diagnosis was delayed in many patients until it was discovered that contaminated material had been injected and the outbreak was publicized [50]. Symptoms and signs of systemic infection are absent in almost all patients.

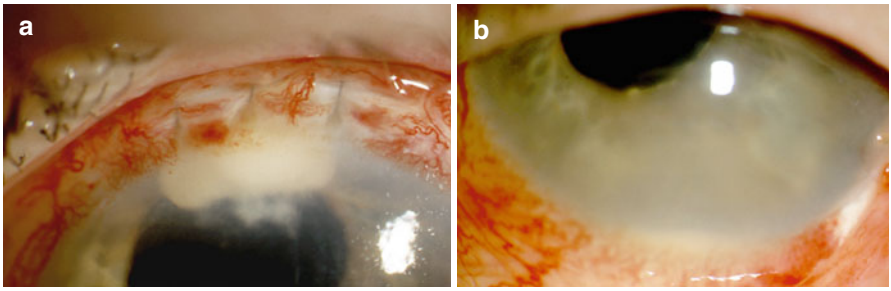


**Fig. 11.1** *Aspergillus* endophthalmitis after cataract surgery. Onset of symptoms was 6 weeks postoperatively; white endothelial plaque was seen at 3 months (**a**), along with a small hypopyon (**b**) (Case described in Ref. [52]; photographs courtesy of Dr. Marlene Durand and Dr. Joan Miller)

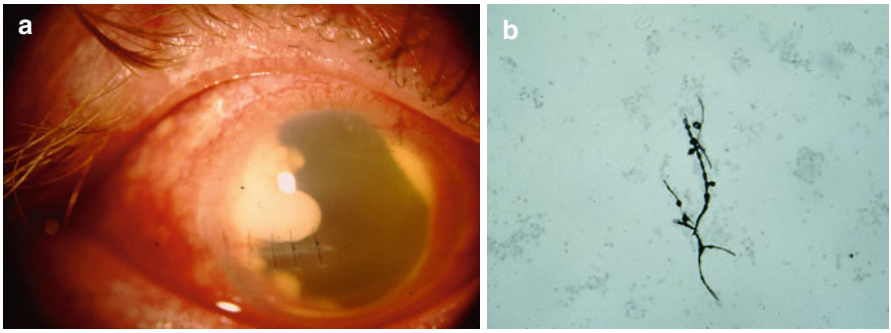


**Fig. 11.2** Mold endophthalmitis with indolent course following penetrating eye trauma (metal fragment) and repair 10 months earlier. At vitrectomy, a white fluffy semisolid material was removed (**a**). Cultures failed to grow, but methenamine silver stain showed hyphae (**b**) (Photographs courtesy of Dr. Marlene Durand)

Examination of the eye shows an entry point if trauma occurred recently and signs of keratitis in those in whom this infection preceded endophthalmitis. Conjunctival injection and corneal edema are commonly noted. Slit lamp examination of the anterior segment reveals white blood cells, flare, and keratic precipitates in many patients [3–5, 48, 49]. In cases of keratitis, frond-like strands may extend from the infected cornea into the aqueous. A hypopyon is present in a majority of patients who have keratitis progressing to endophthalmitis [5, 9], but may be absent in postoperative cases. In one study of 41 patients with exogenous fungal endophthalmitis (85 % due to molds), a hypopyon was seen on presentation in 61 % of keratitis-related cases and 80 % of post-traumatic cases, but in only 8 % of postoperative cases [5]. In some cases, a thick or fluffy white material may be seen in the anterior chamber (Fig. 11.1a, b). Vitritis may be diffuse, giving a cloudy appearance on funduscopic examination, but often has snowballs or a "clumped" appearance (Fig. 11.2a, b). Vitritis was noted in most patients who received contaminated

intraocular injections [50] and in a majority of those with postoperative mold infections in one center [8].

### *11.3.3 Diagnosis*

Culture of the infecting organism is the gold standard diagnostic test for mold endophthalmitis, as it is for *Candida* endophthalmitis [19]. Because preceding keratitis often plays a central role in the pathogenesis of endophthalmitis due to molds, corneal scrapings or biopsy samples should be obtained for both direct smear and staining and for culture. Aspiration of aqueous humor is important for both direct examination and culture. If the posterior segment is involved, an aspirate of the vitreous should be obtained. With involvement of the posterior segment, it is likely that a vitrectomy will be performed and material obtained at operation should be sent for direct examination and culture. A vitrectomy should be performed for diagnosis in cases with vitritis in which fungal endophthalmitis is clinically suspected but vitreous and/or aqueous aspirate cultures are negative.

A tentative diagnosis of a mold infection can be made by examining direct smears on the samples obtained. Gram stain is not useful for molds, but calcofluor white staining is very useful to visualize hyphae [19, 20]. If tissue is obtained, it should be stained with methenamine silver or PAS stains to visualize hyphae. The appearance of most of the hyaline molds is similar – branching septate hyphae. One cannot conclude that *Aspergillus* is the pathogen based only on a stained direct smear because *Fusarium* and *Scedosporium* have a similar appearance. The dematiaceous fungi usually are pigmented, and many times the hyphae are larger and more irregular in appearance. One can only state that a brown-black mold appears to be the pathogen, but diagnosis of a specific organism cannot be made from a smear.

PCR is perhaps more useful for molds than for *Candida* species in that it often can identify an unusual mold more easily than culture techniques [19, 21, 23]. However, none of the PCR assays are standardized, and the sensitivity and specificity are not known. The assay itself is rapid, but availability only in reference laboratories makes rapid diagnosis difficult with this technique.

### *11.3.4 Treatment and Outcome*

The treatment of exogenous endophthalmitis caused by molds is more difficult than the treatment of *Candida* endophthalmitis, in part because the organisms are more resistant to antifungal agents. Fluconazole, the mainstay of systemic treatment for *Candida* endophthalmitis, is not active against molds and plays no role in treatment. The approach to mold infections should be aggressive and include intraocular injection of an antifungal agent, systemic antifungal therapy, vitrectomy in most patients,

and removal of foreign material, such as an IOL. In cases of mold endophthalmitis due to extension of keratomycosis, removal of the infected cornea by penetrating keratoplasty may be necessary.

If infection is localized to the anterior segment, which can be the case with infection secondary to keratitis, intracameral amphotericin B or voriconazole can be used and intravitreal injection may not be necessary in some patients [24–28]. The intracameral dose of amphotericin B is 5 μg in 0.1 mL sterile water, and the dose of voriconazole is 50 μg in 0.1 mL sterile water or saline. The molds that most commonly cause fungal endophthalmitis, *Aspergillus* and *Fusarium,* are usually susceptible to both of these agents. Voriconazole is preferred because it is less irritating than amphotericin B [27, 29].

Administration of voriconazole eye drops, 1 % solution, every 1–2 h, can help sustain the levels of this agent in the anterior chamber because it penetrates through the cornea and achieves levels in the aqueous humor [33]. Amphotericin B eye drops do not penetrate through the cornea as well and are more irritating.

Systemic azole therapy is essential for effective treatment of exogenous mold endophthalmitis. Voriconazole is the treatment of choice because it is active against most molds and because it achieves higher levels in both ocular compartments when compared with the other mold-active azoles, itraconazole and posaconazole [34]. Isavuconazole is a new mold-active azole, but it is unlikely to achieve adequate concentrations in the eye [53]. The experience with voriconazole for treating mold infections in the eye is mostly documented in individual case reports and small series of patients. Most experience is with endophthalmitis due to *Aspergillus* or *Fusarium* [52, 54–56]. For other uncommon molds, voriconazole use is based on in vitro susceptibility of these molds to voriconazole, rather than on extensive clinical experience. In individual case reports, voriconazole has been used with some success in endophthalmitis due to *Paecilomyces lilacinus*, *Scedosporium apiospermum*, *Scopulariopsis* spp., and *Lecythophora mutabilis* [57–63].

The dose of voriconazole is 400 mg twice daily the first day, followed by 200–300 mg twice daily thereafter. Voriconazole has many drug-drug interactions and adverse effects [37]. Serum concentrations should be measured after the first 5 days of therapy and then weekly until the concentrations are deemed appropriate. Serum trough levels between 1.0 and 5.5 μg/mL are adequate for efficacy and decrease the risk of nervous system adverse effects and liver toxicity [64].

There are a few case reports of patients who were successfully treated with oral posaconazole for *Fusarium* endophthalmitis [65, 66]. However, intraocular concentrations are low, and the use of this agent should be discouraged for the treatment of intraocular infections.

If posterior segment involvement is documented, intravitreal injection of amphotericin B, 5–10 μg in 0.1 mL sterile water, or voriconazole, 100 μg in 0.1 mL sterile water or saline, is necessary [34]. Numerous reports note the safety of these agents when given as injections and document improvement in outcomes of mold endophthalmitis when intravitreal injection is performed [3–5, 29, 58, 62, 63, 66].

Vitrectomy should be performed in nearly all patients who have vitreous involvement. This is useful to decrease the number of organisms and to debride any

abscesses that have formed [1, 3, 8, 38]. Intravitreal amphotericin B or voriconazole should be given at the end of the procedure. The half-life of voriconazole and amphotericin B given post-vitrectomy is shorter than when the drugs are injected into an intact vitreous; because of this, a repeat intravitreal injection may be indicated several days after the first.

In general, outcomes of exogenous endophthalmitis caused by molds are poor. The faster the diagnosis is made and aggressive treatment is started, the better the prognosis, but even when diagnosis and treatment move expeditiously, sight is often lost or severely compromised [3, 4, 8].

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# Chapter 12
# Device-Related Endophthalmitis

**Marlene L. Durand and Claes H. Dohlman**

## 12.1 Introduction

The presence of an artificial device in the eye may increase the risk of endophthalmitis. The number of artificial devices is increasing, so device-related endophthalmitis cases are likely to increase as well. The highest risk of endophthalmitis occurs with devices that have a component that crosses the cornea or sclera, such as most types of glaucoma drainage devices and artificial corneas (keratoprostheses). Devices that are entirely intraocular, such as the intraocular lens, have a much lower rate of endophthalmitis and nearly all cases occur in the immediate postoperative period. Devices that have no intraocular component, such as the scleral buckle, rarely cause endophthalmitis. Table 12.1 lists many of the ocular devices in use today.

M.L. Durand, MD (✉)
Department of Medicine, and Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Infectious Disease Service, Massachusetts Eye and Ear, Infectious Disease Unit, Massachusetts General Hospital, Boston, MA, USA
e-mail: mdurand@mgh.harvard.edu

C.H. Dohlman, MD, PhD
Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA
e-mail: Claes_Dohlman@meei.harvard.edu



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**Table 12.1** Artificial devices used in or on the eye

| Device[a] | FDA approval | Manufacturer[b] | Indications[c] |
|---|---|---|---|
| A. *Devices that cross the cornea or sclera* | | | |
| 1. Glaucoma drainage devices | | | Glaucoma |
| Molteno | 1988 | IOP Ophthalmics | |
| Baerveldt | 1991 | Abbott Medical Optics | |
| Ahmed | 1993 | New World Medical | |
| Ex-PRESS mini-glaucoma shunt | 2002 | Optonol | |
| 2. Keratoprosthesis | | | Corneal blindness |
| OOKP | No | N/A | |
| Boston KPro | 1992 | Massachusetts Eye and Ear | |
| Fyodorov-Zuev and Yakimenko (Iakymenko) | No | N/A | |
| 3. Retinal implants | | | |
| Argus II | 2013 | Second Sight | Retinitis pigmentosa |
| Alpha IMS | No (has CE Mark) | Retina Implant AG | Retinitis pigmentosa |
| B. *Intraocular devices* | | | |
| 1. Intraocular Lens | | | |
| Aphakic IOL (post-cataract) | 1981 | Various | Refraction |
| Phakic IOL (e.g., Artisan, Visian Implantable Collamer Lens) | 2004 (Artisan), 2005 (Visian ICL) | Ophtec (Artisan), STAAR Surgical (Visian ICL) | Refraction |
| 2. Intravitreal implants for drug delivery | | | |
| Dexamethasone (Ozurdex) | 2014 | Allergan | Macular edema, uveitis |
| Fluocinolone | | | |
| Retisert | 2005 | pSivida | Uveitis (chronic, noninfectious) |
| Iluvien | 2014 | Alimera Science | Diabetic macular edema |
| Ganciclovir (Vitrasert) | 1996 | Bausch & Lomb (no longer manufactured) | CMV retinitis |
| 3. Intraocular glaucoma micro-bypass stent | | | |
| iStent | 2012 | Glaukos | Glaucoma |
| 4. Artificial iris | | | Aniridia |

**Table 12.1** (continued)

| Device[a] | FDA approval | Manufacturer[b] | Indications[c] |
|---|---|---|---|
| Artificial*Iris* HumanOptics | No | HumanOptics | |
| 5. Implantable Miniature Telescope | 2014 | VisionCare | Bilateral end-stage age-related macular degeneration, age ≥65 |
| C. *Extraocular devices* | | | |
| Scleral buckle | Various | Various | Retinal detachment |
| Contact lens | Various | Various | Refraction, prevent surface drying |

*N/A* not applicable, *FDA* Food and Drug Administration, *OOKP* osteo-odonto-keratoprosthesis, *KPro* keratoprosthesis, *IOL* intraocular lens, *CMV* cytomegalovirus

[a]The list gives examples of each type of device but is not meant to be all-inclusive

[b]In some cases, the original manufacturer is listed

[c]List of indications may not be complete

## 12.2 Devices That Cross the Cornea or Sclera

### *12.2.1 Glaucoma Drainage Devices*

Patients with glaucoma that fails to respond to medications may require either a filtering bleb or a glaucoma drainage device (GDD). The first GDD was the Molteno GDD, approved for use by the Food and Drug Administration (FDA) in 1988 (Table 12.1). The use of GDDs has increased in recent years since they were found to be at least as effective as trabeculectomy for intraocular pressure (IOP) control [1, 2]. The Tube versus Trabeculectomy study, a multicenter trial comparing a GDD with trabeculectomy, found that mean IOP was similar in both groups but the trabeculectomy group had a higher rate of failure (primarily to control IOP) and a resulting higher rate of reoperation for glaucoma (29 % vs. 9 %) [3]. By the 5-year point, endophthalmitis had developed in 1 of 107 (0.9 %) GDD eyes and 2 of 105 (1.9 %) trabeculectomy eyes in that study.

The most commonly used GDDs in the U.S. are Ahmed and Baerveldt, and their efficacy in lowering IOP is similar. A trial comparing these devices found that at 3 years, IOPs were similar in Ahmed and Baerveldt groups although Baerveldt GDDs had a lower rate of failure than Ahmed GDDs (34 % vs. 51 %) but a higher rate of hypotony-related vision-threatening complications (6 % vs. 0 %) [4]. In both devices, a tube used to drain excess aqueous crosses the sclera one or more millimeters behind the limbus and connects to a plate placed on the surface of the globe. The plate and external portion of the tube are covered with various patch graft materials (e.g., pericardium, sclera, cornea, and conjunctiva). Devices are usually placed in the superotemporal location, but may be placed in other quadrants.

The incidence of endophthalmitis in the eyes with GDDs is 1–2 % in studies with 1–5 years of follow-up, with a higher incidence in pediatric patients as discussed below. Exposure of the device due to conjunctival breakdown is a major risk factor

for endophthalmitis [5]. This occurs in approximately 5 % of the eyes during 5 years of postoperative follow-up [3]. Levinson and colleagues reported that 5.8 % of 702 GDDs became exposed over a mean follow-up of 34 months, and the mean time to exposure was 2 years postoperatively [6]. Exposures occurred most often over the tube (88 %) rather than over the plate, and endophthalmitis developed in 1.1 % of patients, all after device exposure.

Implant placement in the inferonasal position may be a risk factor for endophthalmitis. Implants placed in this position had the highest rate of exposure in the Levinson study (17 %), although since most devices (93 %) were placed superotemporally, this did not reach significance [6]. However, exposures over inferior implants were significantly more likely to be associated with endophthalmitis than exposures over superior implants in this study. A study by Rachmiel and colleagues found a higher rate of wound dehiscence and/or conjunctival retraction with exposure of the patch graft in inferior than superior implants (29 % vs. 10 %) [7]. A study by Pakravan and colleagues of 107 eyes (mean follow-up of 10.6 months) found a higher rate of tube exposure requiring GDD explantation in inferior than superior implants (8.3 % vs. 1.7 %), but this did not reach statistical significance [8]. One case of endophthalmitis occurred in this study, and this was in a child with an inferiorly placed implant.

A third risk factor for endophthalmitis is youth, with a higher incidence in the pediatric population. Al-Torbak and colleagues in a study from Saudi Arabia of 545 Ahmed shunts in 505 patients (25 % children) found that 1.7 % of cases overall developed endophthalmitis, but the rate in children was five times higher than in adults (4.4 % vs. 0.9 %) [9]. The onset of infection was 1–11 months postoperatively, and 67 % of cases were associated with conjunctival erosion over the tube. Another study involving 69 eyes of 52 pediatric patients with Baerveldt or Molteno GDD and with mean follow-up of 45 months found that endophthalmitis developed in 5.8 % of the children [10], a rate over five times higher than the study in adults by Levinson and colleagues [6].

Patients with GDD-related endophthalmitis usually present with acute onset of eye pain and decreased vision. Although some cases occur in the immediate postoperative period, most occur months to years postoperatively. This is similar to the timing and clinical features of bleb-related endophthalmitis (see Chap. 8). Systemic symptoms are usually absent, as is the case for nearly all patients with exogenous endophthalmitis. Conjunctival erosion over the tube is often evident. There may be purulence around the tube or the plate, sometimes discovered only at the time of device explantation. Some cases have a more indolent presentation, such as those due to atypical mycobacteria or molds. A patient who developed *Aspergillus* endophthalmitis 7 months after GDD implantation had a month of painless decrease in vision and mild eye redness, illustrating this indolent course [11].

The most common pathogens in GDD-related endophthalmitis are *Streptococcus pneumoniae* and *Haemophilus influenzae*. These two organisms cause most of the infections reported in pediatric patients, while streptococci (including *S. pneumoniae*) and gram-negative bacilli such as *Pseudomonas* are common causes of endophthalmitis in adults. Most reports of GDD-related endophthalmitis are in

the form of case reports so the frequency of various pathogens is hard to assess, but there have been several case series reported. In one series, S. *pneumoniae* and *H. influenzae* caused all four culture-positive pediatric cases, while streptococci (Group B and viridans streptococci) and *Pseudomonas* caused the three culture-positive cases in adults [9]. In another series that included only adults, *S. pneumoniae* (two cases) and coagulase-negative staphylococci (one) caused the culture-positive cases [6] (REF Levinson). A series from Florida of four cases of GDD-related endophthalmitis reported that intraocular cultures in three adult cases were positive in two patients (*Pseudomonas* and *Mycobacterium chelonae*), and negative in a third patient although the explanted GDD grew *S. pneumoniae* and *S. aureus* in that case [12]. The single pediatric case was due to *H. influenzae*. Two other cases of late-onset GDD-related endophthalmitis were excluded from the study because they were culture negative. Concurrent orbital cellulitis and endophthalmitis may occur in some cases of GDD-related infections, particularly in cases due to virulent organisms such as *S. pneumoniae* [13]. Rarely, bacteria that typically cause indolent infections, such as *Propionibacterium* [14], *Nocardia* [15], atypical mycobacteria [12], or molds [11], are causes of GDD-related endophthalmitis. These cases often present subacutely, as noted above.

The treatment for GDD-related endophthalmitis is intravitreal antibiotics; vitrectomy is often necessary given the severity of most infections. We also recommend removal of the infected device, as failures and relapses have occurred when devices have remained in place [16]. If the patient has an artificial intraocular lens as well, consideration should be given to removal of this at the time of GDD removal, especially if endophthalmitis is due to agents associated with indolent infections (e.g., molds, atypical mycobacteria). Repeat injections of intraocular antibiotics may be necessary, depending on clinical response. These repeat injections are usually given at least 2 days after the prior antibiotic injection and tailored to the culture result. The adjunctive role of systemic antibiotics is unknown, but their use may be helpful in treating the soft tissue infection that usually surrounds the external portion of the GDD.

Visual outcome in GDD-related endophthalmitis, as in bleb-related endophthalmitis, is usually poor due to the virulence of the usual pathogens. In the study by Al-Torbak and colleagues, only two of the nine eyes with endophthalmitis achieved 20/200 vision (one culture-negative case and one due to viridans streptococci), while the rest had poor vision including three with no light perception [6]. Good visual outcomes are occasionally achieved, however. In the series by Gedde and colleagues, two out of four cases returned to their baseline visual acuity [12]. Prevention of some cases of GDD-related endophthalmitis cases might be possible through vaccination. We recommend pneumococcal vaccination in all eyes with GDDs and filtering blebs. Vaccination against *H. influenzae* type b is standard for children in the U.S., although this will not protect against the non-typeable strains of *H. influenzae*. A case of *H. influenzae* endophthalmitis was reported in a vaccinated child, but whether this was due to type b or a non-typeable strain was not reported [17]. Since most cases of GDD-related endophthalmitis have occurred after erosion over the tube, prompt surgical repair of any GDD exposure seems prudent and has been previously recommended [12].

### *12.2.2 Keratoprosthesis (Artificial Cornea)*

The keratoprosthesis (KPro), or artificial cornea, is used to give sight to patients with corneal blindness in whom corneal transplantation has failed or is not an option. There is a great need for such a device. The World Health Organization reports that corneal opacity is the fourth leading cause of visual impairment worldwide, following cataract, glaucoma, and age-related macular degeneration [18]. Many patients are affected in developing nations where donor corneal tissue may not be available for transplantation. In developed countries, donor corneas are usually available (>47,500 corneal transplants performed in the U.S. in 2014 [19]), but transplantation is unsuccessful in some ocular conditions. In low-risk conditions such as keratoconus, the 5-year survival probability of a primary corneal transplant is >90 %. However, in high-risk conditions (e.g., corneal endothelial failure after intraocular surgery), graft survival is <50 % [20]. In patients with severe drying conditions such as Stevens-Johnson syndrome (SJS) and ocular cicatrizing pemphigoid (OCP), graft failure rates are known to be high, and corneal transplantation may not be attempted so the "success" rate may in fact be even lower for a given ocular condition. For any condition, graft failure followed by regrafting carries a higher risk of rejection than primary transplantation. Ten to 18 % of keratoplasties are performed for regrafting [20, 21], and the 5-year survival of the first regraft is 50 % overall [20–22], lower in certain conditions (23 % in Fuch's dystrophy [22]) and with any subsequent regraft attempts [20, 22]. Previous glaucoma surgery and corneal neovascularization are risk factors for graft failure [22, 23].

Graft failure is a major indication for KPro implantation and was the indication for 64 % of Boston KPros implanted at a Los Angeles center and 44 % at several international centers [24]. Other major categories of eye conditions for which KPros are placed include chemical or thermal burns, and autoimmune conditions such as SJS and OCP.

A number of different types of KPros have been developed over the years. Several past devices (e.g., Cardona, Worst, Pinducci, Alpha-Cor) have been important for the development of the field but are no longer available. Presently, the three major types in common use are the Boston KPro, the Fyodorov-Zuev KPro (and similar designs), and the osteo-odonto-keratoprosthesis (OOKP). All types of KPros have been associated with a risk of endophthalmitis. Because glaucoma is a common condition in the eyes with KPros, many KPro eyes also have a GDD or filtering bleb, and these may contribute to the risk of endophthalmitis.

In most cases of KPro-related endophthalmitis, the onset of endophthalmitis occurs acutely, months to years postoperatively, similar to the presentation of bleb-related and GDD-related endophthalmitis. Because there is a cumulative risk of endophthalmitis the longer the device is in place, the reported incidence of infection will depend on the duration of follow-up. The mean duration of follow-up is noted below and in Table 12.2.

**Table 12.2** Endophthalmitis in eyes with the Boston keratoprosthesis

| Author (special study features)[a] | Country | Study years | # cases endophthalmitis/# KPros | Topical prophylaxis | Follow-up: mean years (total patient-years) | Endophthalmitis rate (%) | Cases per patient-year | Microbiology |
|---|---|---|---|---|---|---|---|---|
| Nouri [40] (40 % type 2)[a] | USA | 1990–2000 | 13/108 | P-TM or FQ | N/A | 12 % | N/A | Streptococci (8), *S. aureus* (3), coag-neg staph (2) |
| Barnes [48] (27 % type 2), (fungal cases only)[a] | USA | 1990–2004 | 4 fungal cases/202 | V + FQ or FQ only | 2.8 (574) | 2 % | 0.009 | *Candida* (3), *Fusarium* (1) |
| Durand [35] (21 % type 2), (bacterial cases only)[a] | USA | 1990–2006 | 18 bacterial/255 | P-TM or FQ until 1999, then V + FQ | 2.6 (674) | Type 1 = 6 % (0 % on V + FQ); type 2 = 10 % | 0.027 (0.003 in eyes with V+ FQ) | Streptococci (10), *S. aureus* (2), coag-neg staph (3), *Pseudomonas* (1), *Serratia* (1), *Mycobacterium abscessus* (1)[a] |
| Behlau [38] (types 1, 2)[a] | (a) International (b) USA | 2001–2010 | (a) 65/1228 (b) 111/3501 (1990–2010) | N/A | N/A (≥1 year) | (a) 5.0 % international (b) 2.9 % USA | N/A | N/A |
| Fintelmann [45] | USA | 2001–2007 | 4/35 | FQ; V + FQ in some | N/A | 11.4 % | N/A | Coag-neg staph (2), *Pseudomonas* + *S. aureus* (1), NG (1)[b] |
| Ciolino [37] | 18 centers | 2003–2008 | 2/300 | N/A | 1.4 (422) | 0.67 % | 0.005 | Fungus (1), bacteria (1) (isolates not further identified) |

(continued)

**Table 12.2** (continued)

| Author (special study features)[a] | Country | Study years | # cases endophthalmitis/# KPros | Topical prophylaxis | Follow-up: mean years (total patient-years) | Endophthalmitis rate (%) | Cases per patient-year | Microbiology |
|---|---|---|---|---|---|---|---|---|
| Kamyar [89] | USA | 2003–2009 | 0/36 | V + FQ × 6 months then FQ only | 1.4 (50.4) | 0 | 0 | 0 |
| Chan [49] | USA | 2004–2010 | 3/126 | V + FQ | 3.4 (215) | 2.4 % | 0.014 | *Ochrobactrum* (1), *Candida* (2) |
| Ramchandran [47] | USA | 2004–2008 | 10/141 | FQ; V + FQ in some | N/A | 7.1 % | N/A | Coag-neg staph (7), *Providencia* (1), gram-variable coccobacilli (1), no culture (1)[b] |
| Goldman [46] | USA | 2004–2010 | 1/93 | V + FQ × 6 months then FQ only | 2.4 (219) | 1.1 % | 0.005 | MRSA (1), onset at 10 months |
| Greiner [43] | USA | 2004–2010 | 5/40 | V only | 2.8 (112) | 12.5 % | 0.045 | *Pseudomonas* (1), *H. influenzae* (1), *Proteus* (1), *Candida* (1), NG (1)[b] |
| de La Paz [39] (42 % high-risk eyes) | Spain and Germany | 2006–2011 | 8/67 | V + FQ; +P--iodine at clinic visits ≥2010 | 2.2 (147) | 11.9 % | 0.054 | *Candida* (3), streptococci (1), *Brachybacterium* (1), NG (3) |
| Aldave [24] | India,other non-US centers | 2006–2011 | 9/101 | N/A | N/A | 8.9 % | N/A | *Candida* (2), NG (3), no cultures (4) |
| Lekhanont [90] | Thailand | 2006–2013 | 5/42 | N/A | 5.4 (227) | 11.9 % | 0.022 | NG (2), culture-positive not identified (3) |

| Author (special study features)[a] | Country | Study years | # cases endophthalmitis/# KPros | Topical prophylaxis | Follow-up: mean years (total patient-years) | Endophthalmitis rate (%) | Cases per patient-year | Microbiology |
|---|---|---|---|---|---|---|---|---|
| Patel [42] | USA | 2006–2010 | 1/58 | V+FQ, then FQ in low-risk eyes | 1.8 (104) | 1.7 % | 0.010 | *Sphingomonas* (1)[b] |
| Huh [91] (glaucoma drainage devices in all) | USA | 2007–2012 | 1/20 | N/A | 2.6 (53) | 5 % | 0.019 | *Candida* (1)[b] |
| Robert [92, 93] | Canada | 2008–2011 | 1/96 | N/A | 1.6 (153) | 1.0 % | 0.007 | Coag-neg staph (1)[b] |
| de Oliveira [50] | Brazil | 2008–2012 | 0/30 | FQ, P-iodine q 2–3 months | 2.7 (81) | 0 | 0 | 0 |
| Hager [51] | USA | 2008–2013 | 3/24 | V+FQ; P-iodine q3 months ≥2011 | 2.4 (58) | 12.5 % | 0.052 | 3 bacterial (not further identified)[b] |
| Chhablani [94] | India | 2009–2012 | 5/45 | N/A | N/A | 11.1 % | N/A | MRSA (1), *E. coli* (1), *Candida* (1), *Aspergillus* (1), NG (1) |

*S. aureus Staphylococcus aureus*, *coag-neg staph* coagulase-negative staphylococci, *MRSA* methicillin-resistant *S. aureus*, *E. coli Escherichia coli*, *H. influenzae Haemophilus influenzae*, *NG* no growth, *N/A* not available, *P-TM* polymyxin-trimethoprim, *V* vancomycin, *FQ* fluoroquinolone, *P-iodine* povidone-iodine

[a]All studies included only type 1 Boston KPros except for the first four listed

[b]In Durand et al. [35], *M. abscessus* was the only case that occurred during prophylaxis with V+FQ, and this was in a type 2 KPro eye. In Fintelmann et al. [45], three cases occurred while using FQ alone and one while using V+FQ. In Ramchandran et al. [47], all cases occurred after V was stopped. In Greiner et al. [43], two of five cases occurred after a glaucoma drainage device became exposed. In Patel et al. [42], the sole endophthalmitis case occurred in a patient who was not using topical prophylaxis. In Robert et al., the endophthalmitis case occurred while using FQ only. In Hager et al. [51], all cases occurred before P-iodine was introduced

**Fyodorov-Zuev (and Similar) Keratoprosthesis** For over a half-century, Russian and Ukrainian surgeons have implanted a large number of keratoprostheses, particularly in patients blinded by chemical burns or trauma. Fyodorov, Zuev, Moroz, and Glazko [25], and Kalinnikov et al. [26], have employed the Moscow Eye Microsurgery Complex (MICOF) which is composed of a polymethyl methacrylate (PMMA) optical stem and an intrastromal prong of titanium as haptic. The procedure is carried out in two stages. In Ukraine, Yakimenko (also spelled Iakymenko) [27] has championed a similar type of keratoprosthesis. Altogether several thousand devices have been implanted, but very little in terms of outcomes has been published. Still, these devices are fairly widely used, including in other countries [28, 29]. The incidence of endophthalmitis is largely unknown, but in China, Huang et al. [28] reported no cases of endophthalmitis out of 14 KPros implanted for autoimmune diseases (mean follow-up of 3.9 years), and Wang et al. [30] reported seven cases out of 90 MICOF KPros implanted for burns (mean follow-up of 4.8 years). In Iran, Ghaffariyeh reported one endophthalmitis case among ten patients (mean follow-up of 4.3 years) [29]. In Ukraine, Yakimenko (Iakymenko) reported on the experience with 1020 KPros implanted in 1972–2010 (median follow-up 5 years) and found only 19 cases of endophthalmitis [27].

**Osteo-Odonto-Keratoprosthesis (OOKP)** The OOKP device was first introduced in the 1960s by Dr. Benedetto Strampelli in Italy and later refined by Dr. Giancarlo Falcinelli. Most OOKP surgeries have been performed in Italy. The surgery is complex and involves corneal replacement with an optical cylinder of PMMA mounted in a bony (dental) lamina. The surgery has two stages: during stage 1, a tooth and surrounding alveolar bone is removed and formed into a lamina holding an optical cylinder of PMMA; this lamina is then placed into a subcutaneous or submuscular pouch in the contralateral lower lid or similar area for approximately 4 months until stage 2 surgery. Stage 1 also involves harvesting buccal or inner lip mucosa and using this to cover the recipient ocular surface. In stage 2, the OOKP lamina is retrieved and sutured into the eye after corneal trephination and removal of the iris, lens, and anterior vitreous. Unlike some types of KPros, the OOKP may be used in patients with SJS, OCP, and other high-risk ocular surface conditions, and such patients comprise a major portion of OOKP cases in most series. The rate of endophthalmitis varies from 2 to 8 % [31], depending on the series and duration of follow-up. A series from Great Britain of 35 OOKP eyes followed for a mean of 57 months reported nine vitreoretinal complications, including two (6 %) cases of endophthalmitis [32]. The two cases occurred approximately 2.5 years post-implantation, and both followed lamina resorption and optic extrusion. A series from Singapore of 36 OOKP eyes reported two (6 %) that developed endophthalmitis, one immediately postoperatively and one a year later [33]. A series of 181 cases with long follow-up (1–25 years, median 12 years) reported by Falcinelli and colleagues in Italy found only four cases (2 %) of endophthalmitis [34].

**Boston Keratoprosthesis** The Boston KPro was developed at Massachusetts Eye and Ear (MEE) and is the most widely used KPro worldwide, with over 11,000

devices implanted as of 2015. The Boston KPro has been FDA approved since 1992 and has had CE marking in Europe (titanium backplate model) since 2014. The Boston KPro has a collar-button design utilizing a donor cornea, which is sandwiched between a PMMA front plate that includes a central PMMA optical stem, and the backplate which is made of either PMMA or more recently titanium. A titanium locking c-ring is used for backplates made of PMMA; the use of the titanium backplate, FDA approved in 2013, eliminates the need for a locking ring. There are two designs, type 1 and type 2, with type 2 similar to type 1 except it has a 2 mm anterior nub designed to penetrate through the upper lid. Patients who receive a type 2 KPro have a tarsorrhaphy performed several weeks prior to KPro implantation. Type 2 is rarely used (<2 % of KPro devices and these are mostly implanted at MEE) and is reserved for the eyes with severe dryness such as those blinded by SJS. Boston KPros with PMMA backplates are illustrated in Fig. 12.1; the newer type 1 Boston KPro with titanium backplate is illustrated in Fig. 12.2.

Table 12.2 lists the incidence and etiologies of endophthalmitis as reported by various centers; the list is ordered by earliest year of KPro surgery. Nearly all studies include only type 1 KPros. The earliest studies from MEE also included a significant proportion of type 2 KPros, which may be a risk factor for endophthalmitis. The incidence of endophthalmitis was high in the 1990s, partly reflecting the inclusion of a large number of eyes blinded by autoimmune conditions (e.g., SJS, OCP) or burns in those studies. These conditions are now known to be associated with an increased risk of endophthalmitis. Some KPros used during the early 1990s had no backplate holes, which also may have increased endophthalmitis rates (e.g., poor

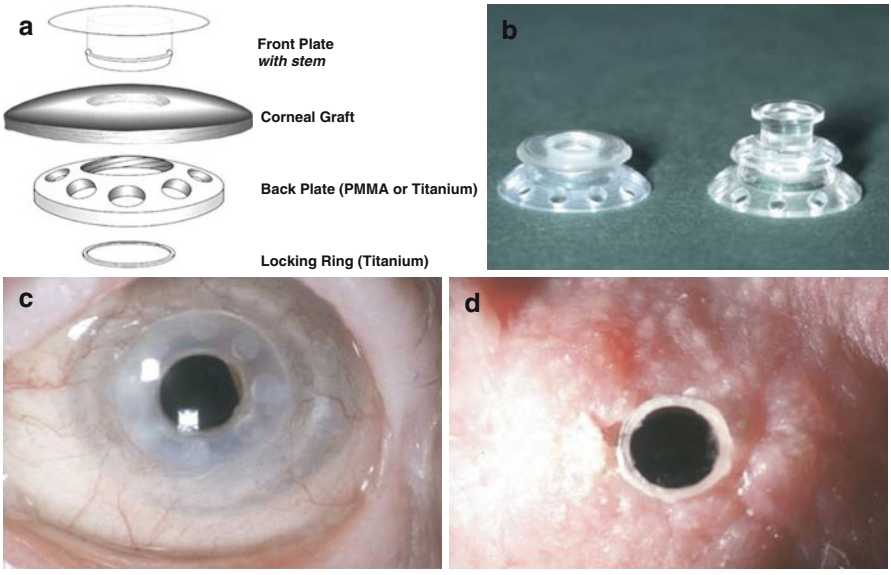


**Fig. 12.1** The Boston keratoprosthesis. (**a**) Diagram of surgical assembly. (**b**) Type 1 and type 2. (**c**) Type 1 in situ. (**d**) Type 2 in situ (Reprinted from Dohlman et al. [95])

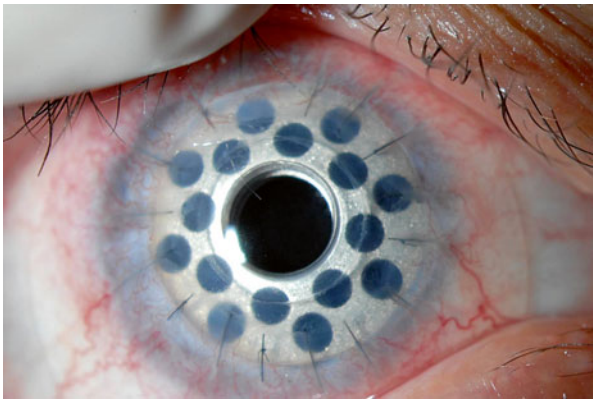

**Fig. 12.2** Boston type 1 keratoprosthesis with titanium backplate (Reprinted from Dohlman et al. [95])

corneal nutrition leading to corneal melts). The addition of vancomycin eye drops to standard topical antibiotic prophylactic regimen [35] and the standard use of bandage contact lenses (BCLs) to prevent drying [36], both introduced in 1999, have led to a low endophthalmitis rate at most centers. In a multicenter study evaluating 300 eyes with type 1 KPros implanted in 2003–2008 at 18 centers (mean follow-up of 1.4 years), the endophthalmitis rate was 0.67 % [37]. Keratoprosthesis retention rates were excellent in that study: 94 % at 1 year and 89 % at 2 years. A surveillance study of 200 U.S. and 106 international KPro surgeons who implanted a combined total of several thousand KPro eyes (>4700 in 1990–2010, at least 1 year follow-up) found that the incidence of endophthalmitis in 2001–2010 was 2.9 % in the U.S. and 5 % in non-U.S. centers [38]. In some centers with high endophthalmitis rates, the rate reflects the large proportion of eyes blinded by conditions associated with an increased endophthalmitis risk (autoimmune, burn). A series from Europe found an 11.9 % endophthalmitis rate, but 42 % of the study eyes were in the high-risk autoimmune or burn category [39]. In an early series from MEE that reported a 12 % endophthalmitis rate, 63 % of study eyes were in high-risk categories (SJS, OCP, burn), and 12 of 13 (92 %) endophthalmitis cases occurred in these high-risk eyes [40]. There was also a high percentage (40 %) of type 2 KPros in this series.

In addition to the autoimmune and burn category of underlying eye conditions, other risk factors for endophthalmitis include the presence of a filtering bleb or GDD, and noncompliance with topical antibiotic prophylaxis. Glaucoma is present in a majority of KPro eyes, and many KPro eyes have pre-existing filtering blebs or GDDs; BCLs may cause erosion of these, leading to secondary infection and subsequent endophthalmitis. This was illustrated in 2002 by a case of bleb-related endophthalmitis due to coagulase-negative staphylococci that occurred after BCL-related bleb erosion [36]. In a study by Li and colleagues, 40 % of KPro eyes had GDDs, and tube erosion was seen in two-thirds of these eyes, in some cases due to trauma from the BCL edge [41]. Two eyes in this study developed endophthalmitis

associated with erosion over the GDD tube. Dohlman and colleagues reviewed 130 KPro eyes with GDDs and found 19 erosions but no cases of endophthalmitis; they noted that some erosions resolved with change to a smaller diameter BCL [42]. However, subsequent to that report, a patient with KPro and Ahmed GDD and with a stable tube erosion for 1.5 years (on polymyxin-trimethoprim prophylaxis) did develop acute *S. pneumoniae* endophthalmitis (C. Dohlman, personal communication). A series from California noted two (one *Pseudomonas*, one culture-negative) of their five cases of endophthalmitis occurred in association with GDD erosions [43]. Endophthalmitis in non-KPro eyes with GDDs following conjunctival erosion over the tube has been well described, as discussed above. Noncompliance with the use of daily topical antibiotic prophylaxis is another risk factor for endophthalmitis. One patient at MEE developed acute streptococcal endophthalmitis 3 days after stopping prophylaxis [35], and the only endophthalmitis case reported in a series from the New York Eye and Ear Infirmary occurred 1 month postoperatively in a patient not using the prescribed topical antibiotics [44].

The onset of KPro-related endophthalmitis is usually delayed, with most cases occurring months to years postoperatively. Symptoms in most bacterial endophthalmitis cases are acute and many patients present with eye pain and decreased vision. Examination shows intraocular inflammation as well as hypopyon in most of these cases. Some cases, particularly those due to more indolent pathogens such as atypical mycobacteria and fungi, have a more indolent presentation with painless decrease in vision and no hypopyon. This was illustrated by the case of a patient with a type 2 KPro who developed endophthalmitis due to atypical mycobacteria: that patient's only symptom was painless vision loss for 4 weeks [35]. Patients with fungal endophthalmitis may also have a subacute presentation, and there is often a history of antecedent fungal keratitis or colonization.

The microbiology of KPro-related endophthalmitis has varied by center and by the prophylactic antibiotic regimen used. Table 12.3 lists the etiology of 19 culture-positive endophthalmitis cases reported by several U.S. and Canadian centers that prescribe broad-spectrum antibiotic prophylaxis (i.e., fluoroquinolone with or without vancomycin). Coagulase-negative staphylococci caused the majority of cases (ten cases, 53 %). Other etiologies were gram-negative bacilli (five cases, 26 %), *S. aureus* (5 %, one methicillin resistant, one in combination with one of the 5 gram-negative cases), and *Candida* (three cases, 16 %). There were no cases of endophthalmitis due to streptococci.

Most endophthalmitis cases have occurred in patients using topical fluoroquinolone prophylaxis alone and almost none in patients using combination therapy with topical vancomycin. Fintelmann and colleagues reported two of four endophthalmitis cases were due to coagulase-negative staphylococci, both occurring after topical vancomycin was stopped [45]. Goldman and colleagues used the combination vancomycin plus fluoroquinolone for 6 months postoperatively and then fluoroquinolone alone: the only case of endophthalmitis in their series of 93 KPro eyes was one due to methicillin-resistant *S. aureus* (MRSA) that developed 10 months postoperatively [46]. Ramchandran and colleagues reported ten cases of endophthalmitis, seven due to coagulase-negative staphylococci, and all occurred while the eyes were

**Table 12.3** The microbiology of culture-positive cases of endophthalmitis occurring in type 1 Boston KPro eyes implanted at U.S. and Canadian centers after 2000[a]

| Author | Total KPros | Coagulase-negative staphylococci | *Staphylococcus aureus* | Streptococci | Gram-negative bacilli | *Candida* | Total |
|---|---|---|---|---|---|---|---|
| Fintelmann [45] | 35 | 2 | (1)[b] | 0 | 1[b] | 0 | 3 |
| Chan [49] | 126 | 0 | 0 | 0 | 1 | 2 | 3 |
| Ramchandran [47] | 141 | 7 | 0 | 0 | 2 | 0 | 9 |
| Goldman [46] | 93 | 0 | 1[c] | 0 | 0 | 0 | 1 |
| Patel [44] | 58 | 0 | 0 | 0 | 1 | 0 | 1 |
| Huh [91] | 20 | 0 | 0 | 0 | 0 | 1 | 1 |
| Robert [92, 93] | 96 | 1 | 0 | 0 | 0 | 0 | 1 |
| Kamyer [89] | 36 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 569 | 10 | 1, plus 1 with gram negative | 0 | 5 | 3 | 19 |

[a]The table includes results from centers that prescribed broad-spectrum topical antibiotic prophylaxis, such as fluoroquinolone with or without vancomycin, and that listed microbiologic results. Not included are studies that reported endophthalmitis incidence but not the identity of the pathogens (e.g., Ciolino [37], Behlau [38], Hager [51])
[b]Cultures grew both *Pseudomonas* and *Staphylococcus aureus*
[c]Cultures grew methicillin-resistant *S. aureus* (MRSA)

still receiving fluoroquinolone eye drops but after topical vancomycin prophylaxis was stopped [47]. Fungal endophthalmitis cases have been more prevalent since 2000, particularly in the eyes receiving broad-spectrum antibiotics plus corticosteroids plus BCLs, a combination that favors fungi. It is possible that the eyes blinded by autoimmune conditions (SJS, OCP) are at higher risk for fungal endophthalmitis than the eyes with other preoperative conditions. In a study from MEE of KPro-related fungal keratitis and endophthalmitis, 70 fungal surveillance cultures were obtained from 36 eyes (31 % with autoimmune conditions), and four of the six cases that grew fungi (*Candida*) occurred in autoimmune eyes [48]. None of these eyes developed endophthalmitis, but two of the three *Candida* endophthalmitis cases in that study occurred in autoimmune eyes. In a study from Cincinnati of 126 KPro eyes, two of the three endophthalmitis cases were due to fungi (*Candida*), and both *Candida* cases occurred in the eyes blinded by SJS [49]. Autoimmune eyes are at higher risk for any type of endophthalmitis, however; it is unclear if they are at higher risk for fungal than bacterial infections.

The visual outcomes of KPro patients with endophthalmitis have been variable, with poor outcomes often resulting from infection due to virulent organisms. Many cases of coagulase-negative staphylococci have achieved good visual outcomes, while endophthalmitis due to streptococci, *S. aureus*, or gram-negative bacilli may result in blindness.

Prevention of endophthalmitis remains an important goal. The optimal prophylaxis is not yet known, but long-term daily topical antibiotic prophylaxis seems

essential. For low-risk eyes, a broad-spectrum topical antibiotic such as polymyxin-trimethoprim is recommended, and this may be tapered down postoperatively to once-daily usage. A study that reviewed the MEE KPro experience in 2007–2010 using topical polymyxin-trimethoprim prophylaxis in low-risk eyes (non-autoimmune, non-burn; 30 patient-years cumulative follow-up) found only one case of bacterial endophthalmitis and that occurred in a noncompliant patient; there were no cases of fungal keratitis or endophthalmitis [38]. For monocular patients or high-risk eyes (autoimmune or burns), topical vancomycin plus fluoroquinolone is recommended. Topical vancomycin alone is not recommended and has been associated with a higher rate of gram-negative endophthalmitis [43]. The addition of topical povidone-iodine, given at clinic visits, and/or short courses of topical antifungal eye drops given periodically (e.g., every 3 months) may prevent some fungal cases, but the efficacy is unknown. Tapering off topical corticosteroids, when possible, may also reduce the incidence of fungal endophthalmitis. In a series from Brazil (mean follow-up of 2.7 years), corticosteroids were rapidly tapered postoperatively, and patients used daily topical fluoroquinolone plus periodic povidone-iodine (instilled at clinic visits every 2–3 months): no eyes developed endophthalmitis [50]. Centers in Iowa, Spain, and Germany have also found that the addition of intermittent topical povidone-iodine to standard daily antibiotic prophylaxis is beneficial in reducing endophthalmitis rates [39, 51].

### *12.2.3 Retinal Implants*

A number of retinal implants are in development, but as of mid-2015, only two are commercially available and only one is FDA approved. The Argus II device (Second Sight Medical Products, California) was FDA approved in 2013 and also has CE marking (2011). The Alpha IMS (Retina Implant AG, Germany) has CE marking (2013) but is not yet FDA approved. All other devices (e.g., Boston Retinal Implant, Epi-Ret 3, Intelligent Medical Implants) are in clinical trials or are still being tested in animal studies [52]. Both Argus II and Alpha IMS have a component that crosses from the retina (epiretina in Argus II, subretina in Alpha IMS) to the surface of the sclera.

**Argus II** The Argus II system consists of an active device implanted on and in the eye as well as external equipment worn by the patient [53]. The internal component consists of a surgically implanted scleral band that contains an electronics package and a receiving antenna, and an intraocular electrode array that is placed via a sclerotomy and tacked epiretinally (over the macula). The patient wears a glasses-mounted video camera and small video-processing unit that sends data and power wirelessly from a transmitting antenna on the glasses to the internal receiving antenna on the scleral band. A total of 30 patients received the Argus II between June 2007 and August 2009 at ten different centers in the U.S. and Europe [53]. Over the 3 years of follow-up, keratitis occurred in one patient (3 %), conjunctival erosion occurred in four patients (13 %), conjunctival dehiscence in three patients (10 %), and endophthalmitis in three patients (10 %). All three endophthalmitis

cases were culture-negative and were successfully managed medically; none were associated with conjunctival erosion. Two of the three cases resulted from devices that had been placed at the same center on the same day. All three cases occurred within the first 2 months postoperatively and within the first year of the start of the study. The protocol was changed after these cases to include prophylactic intravitreal antibiotics at the end of each case, and no further cases of endophthalmitis occurred [53].

**Alpha IMS** The Alpha IMS device has a 3 × 3 mm vision chip (multi-photodiode array) on a polyimide foil, both placed subretinally [54]. The foil exits the eye in the upper temporal periphery through the choroid and sclera. The foil is connected on the sclera to the power supply cable, which leads to a retroauricularly placed subdermal coil. The subdermal coil receives energy and signals via transdermal electric induction from an external coil which is magnetically held in place behind the ear, and which is connected to a battery pack. A study of 29 patients with up to 1 year of follow-up reported only two serious adverse events: an increase of intraocular pressure and retinal detachment [55]. An earlier report of adverse events seen during 1 year of follow-up in the first nine patients implanted (implanted in 2010–2011) noted that recurrent conjunctival erosions occurred in some patients and this problem subsequently resolved after the extraocular component was covered with a scleral transplant [56]. No cases of endophthalmitis have been reported.

## 12.3 Intraocular Devices

### *12.3.1 Intraocular Lenses*

Intraocular lenses (IOLs) placed during cataract surgery may contribute to postoperative endophthalmitis. Over a million IOLs are placed annually in the USA. The earliest intraocular lenses were rigid and made of PMMA, but since then, foldable (e.g., acrylic, silicone) lenses have been manufactured. Biofilms may develop on these lenses, especially caused by *P. acnes* and coagulase-negative staphylococci [57]. The most commonly used IOL materials are hydrogel, acrylic, silicone, and PMMA, and various experimental studies confirm the ability of bacteria to form biofilms on any of these materials. Hydrophilic lens materials may be less prone to biofilm formation than hydrophobic lenses [57, 58]. Cases of chronic low-grade endophthalmitis and cases with recurrent endophthalmitis due to the same organism have been attributed to biofilms on the IOL. In a case of postoperative enterococcal endophthalmitis that was treated but recurred 4 months later, the explanted IOL was found to harbor a biofilm of the bacteria [59]. Biofilms are discussed further in Chap. 3, and postoperative endophthalmitis is discussed in Chap. 5.

Phakic IOLs, sometimes referred to as implantable contact lenses, have been FDA approved for over 10 years. Device types include those that insert into the

anterior chamber (such as types that attach to the iris) or posterior chamber (such as the Implantable Collamer Lens). Complications of these devices include cataract formation, elevated intraocular pressure, and endothelial cell loss [60, 61]. Rare cases of postoperative endophthalmitis have been described, including cases due to Group B Streptococcus [62], *Rhizobium radiobacter* [63], atypical mycobacteria [64], and *Aspergillus* [65]. The rate of endophthalmitis and the major pathogens are unknown, but a survey of surgeons who implanted the Implantable Collamer Lens (STAAR Surgical, California) found three cases in the nearly 18,000 procedures performed, for a rate of 0.017 % [66]. Cultures were reported for two of the cases and grew coagulase-negative staphylococci.

### *12.3.2 Intravitreal Implants for Drug Delivery*

Intravitreal implants for sustained-release drug delivery have been FDA approved for approximately 20 years. The ganciclovir implant was one of the first such implants (1996), but it is no longer available in the U.S., where CMV retinitis is now rare. Implants for corticosteroid delivery have been developed, primarily to treat noninfectious uveitis and macular edema, and these overcome the relatively short half-life of injected corticosteroids (approximately 3 h) and need for repeated injections [67]. We will discuss one such implant here, Ozurdex (Allergan, California). Boyer and colleagues recently reported 3-year pooled results for two phase III trials (1048 eyes, nearly 3000 injections) of the Ozurdex implant for patients with diabetic macular edema [68]. Patients were randomized to three groups, DEX 0.7 mg, DEX 0.35 mg, or sham. There was one treatment-related case of endophthalmitis; another case occurred but was attributed to cataract surgery. Ryder and colleagues reported outcomes in 11 patients with bilateral Ozurdex implants (DEX 0.7) placed for treatment of noninfectious posterior uveitis and macular edema secondary to retinal vein occlusion: there were no cases of endophthalmitis [69].

### *12.3.3 Intraocular Trabecular Micro-bypass Stent (iStent)*

Open-angle glaucoma is the major cause of irreversible vision loss worldwide, and devices used for minimally invasive glaucoma surgery (MIGS) are gaining in popularity. One MIGS device is the iStent (Glaukos, California), which was FDA approved in 2012 to be used in conjunction with cataract surgery to treat mild to moderate open-angle glaucoma. This device lowers the IOP by directly cannulating Schlemm's canal and enhancing the aqueous outflow. The iStent is entirely intraocular. A review of published iStent series concluded that the major complications were early postoperative stent occlusion and malposition [70]. No cases of endophthalmitis have been reported to date.

### 12.3.4 Prosthetic Iris Implants for Aniridia

A prosthetic iris implant for aniridia was first used in 1964 [71]. Many iris devices to treat congenital or traumatic iris defects have since been developed [72]. None are yet FDA approved, but several have CE marking and have been used in Europe for many years. A device to correct both aniridia and aphakia, the iris-lens diaphragm, was first used in 1991 [73]. This device was developed in cooperation with Morcher GmbH (Stuttgart, Germany), and Morcher has several types of black-diaphragm irises commercially available in Europe. A phase I FDA trial in the U.S., sponsored by the University of California, Los Angeles, of the Morcher artificial iris began in 2002, but only 61 patients were enrolled as of 2012 [74]. The Morcher artificial iris used in this trial is designed to be placed in the capsular bag in an aphakic patient, in front of an IOL. An artificial iris-IOL combination available in Europe is Artisan Iris Reconstruction IOL made by Ophtec (Groningen, The Netherlands). A customized artificial iris without IOL has been commercially available in Europe for several years, Artificial*Iris* made by HumanOptics AG (Erlangen, Germany). This device is made of flexible silicone and custom colored to match the patient's other eye. The device is known as CustomFlex Artificial Iris Prosthesis in the U.S., where there is a phase III multicenter trial currently ongoing (started 2013). Complications of therapeutic iris implants include glaucoma, anterior uveitis, and malpositioning of the implant. A single case of endophthalmitis after artificial iris implantation has been reported, and this occurred 3 days after implantation of the Morcher prosthetic iris [75]. The culture in that case was negative, but the Gram stain showed gram-positive cocci. A 2014 review of 23 publications with a total of 279 artificial iris implants found only this one case of endophthalmitis [72].

Iris implants for cosmetic use have been made by a company in Panama and are widely discredited due to the potential for serious, vision-threatening complications [76, 77]. Companies that manufacture therapeutic iris implants specifically note that their lenses may not be used for cosmetic purposes.

### 12.3.5 Implantable Miniature Telescope

A miniature telescope, Implantable Miniature Telescope (VisionCare Ophthalmic Technologies, California), was FDA approved in 2014 for use in patients age 65 and older with bilateral end-stage age-related macular degeneration. The device uses a fixed-focus telescopic system that enlarges the visual objects in a patient's central vision. Because the peripheral field is reduced, the device is implanted in one eye only, allowing the other eye to provide peripheral vision. The surgery involved is similar to standard phacoemulsification but with a larger incision. A prospective trial of 197 patients with long-term (up to 5-year) follow-up found that the most common complications were iritis and corneal edema; endothelial cell density loss was 3 % per year and reportedly similar to that reported for conventional IOLs [78]. There were no cases of endophthalmitis.

## 12.4 Ocular Surface Devices

### *12.4.1 Scleral Buckles*

Scleral buckles, placed for treatment of retinal detachment, may become infected in the immediate postoperative period or, more often, months to years later, usually after partial extrusion and secondary infection. Orbital cellulitis is the most common infectious complication of an infected scleral buckle but even this is rare. In a series of 841 scleral buckles placed at a center in Israel, 40 (5 %) were removed over a 20-year period but only 16 (2 %) for infection [79]. Seven of these 16 cases had orbital cellulitis; no cases of endophthalmitis were reported. A study from India of 132 patients who underwent scleral buckle removal for infection found five with endophthalmitis (including three with panophthalmitis) [80]. The median time postoperatively to symptom onset ranged from 1 day to 5 years, and 82 % had evidence of exposed buckle or suture on presentation. Most exposed buckles were solid rather than sponge type. Cultures of the five cases of endophthalmitis were not specifically reported, but the major organisms recovered from explanted buckles were coagulase-negative staphylococci (22 %), gram-negative bacilli (16 %), atypical mycobacteria (16 %), fungi (14 %), and *Corynebacterium* species (10 %). Virulent gram-positive pathogens such as *S. aureus* (6 %) and *S. pneumonia*e (4 %) were less common. In another series from India of 24 patients who underwent buckle explantation, patients presented with buckle extrusion, a mean of 7.5 years postoperatively [81]. The most common pathogens in culture-positive cases were atypical mycobacteria (26 %), *Corynebacterium* species (21 %), *S. aureus* (16 %), molds (16 %), and *Pseudomonas* (11 %). Two cases of endophthalmitis occurred with buckle explantation, and these were due to *M. chelonae* and *Aspergillus*. Hydrogel scleral buckles had significant complications from expansion and were removed from the market in 1995, but some cases of globe penetration resulting in evisceration are still reported [82]. Endophthalmitis may occur secondary to this penetration. This was illustrated in a recent case report of *H. influenzae* endophthalmitis that resulted from globe penetration by a hydrogel buckle placed 25 years earlier [83]. Although most cases of endophthalmitis related to scleral buckles are delayed onset, acute postoperative scleral buckle infection may rarely occur. Oshima and colleagues reported seven cases of acute postoperative MRSA infections in 293 eyes implanted with scleral buckles over a 2-year period; three of these MRSA cases also had endophthalmitis [84].

### *12.4.2 Contact Lenses*

The Centers for Disease Control and Prevention (CDC) estimates that 40.9 million (16.7 %) U.S. adults wear contact lenses. A recent survey of 1,000 contact lens wearers found that 99 % report having used poor contact lens hygiene at some point, such

as rinsing or storing lenses in water (36 % and 17 % of respondents, respectively), practices that have been associated with eye inflammation or infection [85]. One-third of those surveyed reported at least one health care visit for a red or painful eye while wearing lenses. Contact lenses, unlike the other devices discussed above, are removable and are not directly associated with cases of endophthalmitis. However, contact lens wear is a major risk factor for keratitis, and rarely keratitis may progress to endophthalmitis. Cases of keratitis-related endophthalmitis are rare and are almost always due to fungi. In a series of 49 patients with keratitis-associated endophthalmitis, 27 had primary keratitis (i.e., not associated with a prior surgical wound), and 78 % of these cases were due to fungi [86]. Only three cases were associated with contact lens wear, and all three had fungal infections. An international outbreak of contact lens-related *Fusarium* keratitis occurred in 2005–2006 and was associated with a specific lens cleaning solution [87]. Some cases progressed to endophthalmitis [88].

## 12.5 Conclusion

Many devices are now available for use in or on the eye, and the presence of a foreign material may increase the risk for infection. For devices that are intraocular only, endophthalmitis is rare and most cases occur in the immediate postoperative period. For extraocular devices such as scleral buckles, the risk of endophthalmitis occurs primarily after extrusion of the device. For devices that cross the sclera or cornea, there is a risk for endophthalmitis in the postoperative period but also an ongoing risk if a component of the device becomes exposed. For GDDs, endophthalmitis risk can be minimized by prompt repair of any conjunctival breakdown over the tube or plate. For Boston KPros, the surface of the device is always exposed, but many centers have achieved a very low rate of endophthalmitis with a protocol that includes the daily use of broad-spectrum topical antibiotic prophylaxis. Efforts are ongoing to determine the optimal prophylaxis for each device.

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# Chapter 13
# Endophthalmitis in Immunocompromised and Diabetic Patients

**Yingna Liu, Ann-Marie Lobo, and Lucia Sobrin**

## 13.1 Introduction

A major consequence of an immunocompromised state is an increased frequency and severity of infection. Some medical conditions are associated with an immunocompromised state, most notably human immunodeficiency virus infection (HIV)/acquired immunodeficiency syndrome (AIDS) and hematologic malignancies. In other cases, an immunosuppressed state is iatrogenic, such as in transplant patients and patients with rheumatologic conditions on chronic immunosuppressive agents. Because of their susceptibility to bacteremia and fungemia, immunocompromised individuals are at increased risk for endogenous endophthalmitis. Among hospitalized patients with bacteremia or fungemia, endogenous endophthalmitis is rare (0.05–0.4 %) but is associated with several comorbid conditions, including HIV/AIDS, lymphoma/leukemia, and diabetes [93]. The types of endophthalmitis, clinical features, differential diagnosis, and microbiology differ depending on the immunocompromising condition.

Y. Liu
Harvard Medical School, Boston, MA, USA

A.-M. Lobo, MD
Department of Ophthalmology, University of Illinois College of Medicine at Chicago, Chicago, IL, USA

Illinois Eye and Ear Infirmary, Chicago, IL, USA
e-mail: alobo2@uic.edu

L. Sobrin, MD, MPH (✉)
Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear and Massachusetts General Hospital, Boston, MA, USA
e-mail: Lucia_Sobrin@meei.harvard.edu



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## 13.2 Endophthalmitis in HIV/AIDS Patients

As of September 2013, 35.3 million people were estimated to be living with HIV/AIDS, an infection characterized by impaired cell-mediated immunity as a result of the viral destruction of CD4 T-helper cells. Despite widespread use of highly active antiretroviral therapy (HAART) in the industrialized world, HAART is unavailable to many patients in developing nations. Ocular manifestations of AIDS affect 50–75 % of untreated HIV-positive patients at some point in their lifetime [45]. Retinal microvasculopathy is the most common ocular manifestation of AIDS, affecting between 40 and 60 % of untreated HIV-positive patients, and cytomegalovirus (CMV) retinitis is the most common cause of vision loss [45, 95]. Endophthalmitis, on the other hand, is rare in patients with HIV/AIDS, even those with low CD4 counts. In a study from Ethiopia of 348 HIV-positive patients, half of whom were receiving antiretroviral therapy, the overall prevalence of ocular manifestations was 25 % but nearly all were adnexal or anterior segment conditions, while HIV retinopathy occurred in only 0.6 %, and there were no cases of endophthalmitis [8].

Because endophthalmitis is rare in HIV/AIDS, it is particularly important to consider a broad differential diagnosis. Other diseases that have signs and symptoms that could overlap with those seen in endophthalmitis in HIV-infected patients include CMV retinitis, ocular syphilis, *Toxoplasma* chorioretinitis, immune recovery uveitis, acute retinal necrosis, progressive outer retinal necrosis, and medication-associated etiologies such as rifabutin-induced hypopyon uveitis.

### *13.2.1 Exogenous Endophthalmitis*

Patients with HIV can develop exogenous endophthalmitis from ocular trauma, eye surgery, or an extension of keratitis. In such cases, aqueous humor may be seeded first before extension into the vitreous. Cataract surgery is becoming increasingly common in treated and virally suppressed HIV-positive patients as they age: such patients now have a life expectancy approaching that of HIV-negative patients [61]. The age-related risk of developing a cataract is higher in the HIV-positive population [44]. HIV-infected patients also have a higher risk of developing a cataract for factors other than aging, for example, if they have a history of prior intraocular inflammation from CMV retinitis. A Danish study of 5315 HIV-infected patients found that the higher risk of cataract surgery was in patients with a CD4 count of 200 or less [76]. Whether or not the rate of post-cataract endophthalmitis is higher in HIV-infected patients who undergo cataract surgery than in uninfected patients has not been reported.

One important etiology of exogenous endophthalmitis in HIV patients is that associated with intravitreal antiviral injections and ganciclovir implant procedures for CMV retinitis, a condition seen primarily when the CD4 count is less than 50 cells/μl. The treatment for CMV retinitis is systemic antiviral medications with

activity against CMV (e.g., valganciclovir), with an initial intravitreal injection of ganciclovir or foscarnet for severe or macula-threatening infections. Rarely do these injections need to be repeated more than once in patients treated with effective systemic anti-CMV medications. However, developing countries that cannot afford systemic anti-CMV antibiotics may treat CMV retinitis with intravitreal ganciclovir injections given weekly for "maintenance" therapy indefinitely after initial twice-weekly induction therapy [90]. There is a small risk of endophthalmitis with each injection. The incidence of endophthalmitis after intravitreal injections varies from 0 to 5 % depending on total number of injections included [5–7, 90, 103]. Ideally the incidence should be reported as events per injection. A large multicenter study reported a rate of 0.012 endophthalmitis cases per injection, or 1.2 % [38], which is much higher than the endophthalmitis rate of 0.04 % after anti-VEGF injections in the general population [84]. Coagulase-negative staphylococci and viridans streptococci have been the most common pathogens reported after anti-CMV injections [19, 103], similar to the microbiology of endophthalmitis following anti-VEGF injections.

CMV retinitis has also been treated with ganciclovir intraocular implants, although these implants are no longer available in the U.S. as manufacture ceased in 2014. There is little demand for ganciclovir implants in developed countries, both because CMV retinitis is now rare in these countries due to HAART and because the treatment of choice for CMV retinitis is systemic anti-CMV medications (plus immune reconstitution with HAART). When ganciclovir implants were available, however, there was a known though small risk of exogenous endophthalmitis following implantation. Large series (including >100 ganciclovir implants) reported endophthalmitis rates of 0.36–1.6 % [38, 43, 66]. In a survey of 30 clinical practices in the U.S. involving 5185 implants, endophthalmitis developed in 0.46 %, with two-thirds of cases occurring within the first 30 days postoperatively [81]. Late cases occurred primarily due to wound issues such as an extruded implant. All culture-positive vitreous samples grew gram-positive bacteria, with coagulase-negative staphylococci accounting for 40 %. Other studies have also reported that coagulase-negative staphylococci and viridans streptococci are common pathogens in this infection, although rare cases due to fungi have been reported [54]. The treatment of exogenous endophthalmitis in HIV-infected patients is the same as in immunocompetent patients: intravitreal antibiotic therapy as soon as possible. The addition of systemic antifungal antibiotics is usually indicated in fungal endophthalmitis cases.

### *13.2.2 Endogenous Endophthalmitis*

The more common type of endophthalmitis in the HIV/AIDS population is endogenous, particularly in intravenous drug users (IVDU). Patients who abuse IV drugs are at increased risk for transient bacteremia or fungemia and subsequent endogenous endophthalmitis. Injection drug use is also a risk factor for HIV, and almost one-third of patients in a series of endophthalmitis in IVDU patients had HIV [69].

Cases of endogenous endophthalmitis in AIDS patients have been described for nearly 30 years [35], with fungal endophthalmitis comprising the majority of cases.

The usual presentation of fungal endophthalmitis is subacute, and the patient may present with painless, subtle vision loss with near normal visual acuity. In advanced cases, the patient usually presents with eye pain and significant vision loss. Endophthalmitis can involve one eye or both eyes. In fungal endophthalmitis, findings on examination range from chorioretinitis (especially in *Candida* endophthalmitis) to endophthalmitis with significant vitritis. Focal, white, infiltrative, often mound-like lesions on the retina may be seen, and borders may be indistinct giving a fuzzy appearance. When vitreous extension occurs, fluffy white balls or a "string of pearls" in the vitreous can be noted. A hypopyon may be present.

*Candida* endophthalmitis in HIV-positive patients is usually associated with other concurrent risk factors such as indwelling central venous catheters or IVDU [71]. Cases secondary to skin or urinary tract infections also have been described [35, 57]. Treatment for *Candida* endophthalmitis includes systemic antifungal agents combined with intravitreal antifungal agents (amphotericin B or voriconazole), with or without vitrectomy depending on the degree of vitritis and response to intravitreal injection. *Candida* chorioretinitis often responds to systemic antifungal treatment alone.

*Aspergillus* endophthalmitis is an important disease in HIV/AIDS due to its severity. Species reported include *Aspergillus fumigatus*, *niger*, *conicus*, and *versicolor* [70, 73, 86]. Endogenous *Aspergillus* endophthalmitis may have an acute or subacute presentation. Cases presenting with several weeks of painless, gradual vision loss have been described [86]. Treatment is the same as for HIV-negative patients and is discussed in Chap. 10. In general, *Aspergillus* endophthalmitis is associated with a poor visual outcome, especially when there is macular involvement, but cases of complete visual recovery have been described [86].

*Fusarium* endophthalmitis is the second most common cause of mold endophthalmitis worldwide, after *Aspergillus*. It most commonly arises exogenously in immunocompetent patients. In HIV/AIDS, *Fusarium* endophthalmitis can be endogenous, as in the reported case of an AIDS patient with bilateral eye involvement [33]. Histopathology showed severe necrotizing and granulomatous reaction, as well as angiopathic infiltration and widespread thrombosis causing retinal and choroidal infarction. Treatment is usually with vitrectomy, intravitreal amphotericin B, or voriconazole, plus oral voriconazole.

Some uncommon fungi have also been reported in HIV/AIDS-associated endophthalmitis. Disseminated *Sporothrix* infections have been reported in two cases, one due to *S. schenckii* [49] and the other due to *S. brasiliensis* [85]. Unfortunately, both patients lost sight despite antifungal therapy.

Cryptococcal endophthalmitis is rare but has been described in AIDS patients, often associated with concurrent cryptococcal meningitis or severe disseminated infection [23]. Two cases associated with immune reconstitution inflammatory syndrome (IRIS) have been described [56, 83].

Endogenous bacterial endophthalmitis is relatively uncommon compared to fungal endophthalmitis. A review of 342 endogenous bacterial endophthalmitis cases reported in the literature 1986–2012 included 12 (3 %) in patients with HIV/AIDS [39]. Various pathogens have been reported in HIV patients, including *S. aureus*,

streptococci (including *S. pneumoniae*), gram-negative bacteria such as *Neisseria gonorrhoeae*, *Serratia* and *Salmonella*, and atypical mycobacteria such as *Mycobacterium avium* [4, 13, 18, 30, 31, 48, 79, 101]. Treatment is the same as for HIV-negative patients (see Chap. 10).

## 13.3 Endophthalmitis in Transplant Patients

Organ transplantation has increased worldwide since the first successful human kidney transplant in 1954. As a result of a number of advancements including more effective immunosuppressive agents, graft survival has improved and patients with transplants are living longer than ever. At the same time, an immunosuppressive state and its complications have become main barriers to disease-free survival after successful transplant procedures. Unfortunately, endophthalmitis is one of these complications, and in some cases it is a manifestation of a potentially fatal disseminated infection.

The differential diagnosis for endophthalmitis in transplant patients depends on the clinical setting (e.g., postoperative or presumed endogenous) and the eye examination. For endogenous cases the differential may include CMV retinitis, toxoplasmic chorioretinitis, ocular syphilis, acute retinal necrosis, and progressive outer retinal necrosis.

### *13.3.1 Exogenous Endophthalmitis*

Corticosteroid-induced cataracts are common in the transplant population, occurring in more than 15 % of patients. It is unknown whether transplant patients have an elevated risk of post-cataract endophthalmitis compared with the general population. Patients with allogeneic hematopoietic stem cell transplant (HSCT) have a 40–60 % chance of developing ocular graft-versus-host disease [63], with keratoconjunctivitis sicca and cicatricial conjunctivitis as common manifestations. These patients are at risk for corneal ulcers with subsequent perforation and exogenous endophthalmitis, although the incidence of the latter has not been determined [1].

### *13.3.2 Endogenous Endophthalmitis*

Endogenous fungal endophthalmitis accounts for 15–22 % of ocular complications in patients with solid organ or HSCT [15, 65]. About 0.1–0.5 % of transplant patients develop fungal endophthalmitis [15, 65]. The onset of infection is within 1 year in nearly all cases. The eye infection may be clinically silent at first, but then the patient develops blurred vision with or without eye pain. Fever and other systemic symptoms of the fungemia may be present. On examination, the fluffy white lesions of chorioretinitis may be seen in the posterior pole, and this may be the only finding initially in

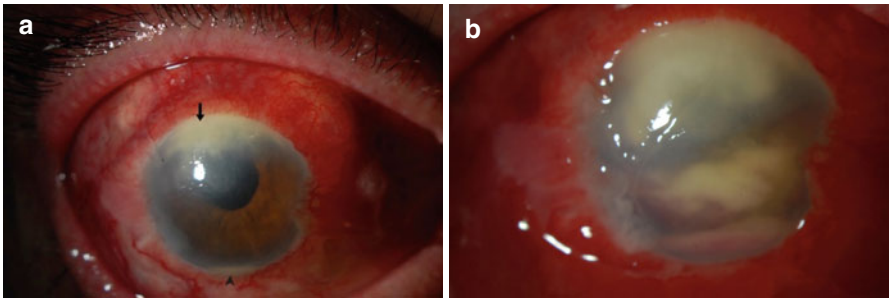


**Fig. 13.1** A 63-year-old man who had undergone a liver transplant and was being treated with mycophenolate and cyclosporine presented with pain and redness 1 week after biopsy for possible recurrent conjunctival squamous cell carcinoma. The biopsy had not shown any malignant cells. (**a**) On examination, he had a superior corneal infiltrate (*black arrow*) and a hypopyon (*black arrowhead*). There was a limited view to the fundus but ultrasound revealed vitreous debris. The patient underwent vitrectomy, lensectomy, and multiple injections of amphotericin and voriconazole into the vitreous and anterior chamber. Cultures of anterior chamber and vitreous revealed *Paecilomyces* species. (**b**) Despite therapy, his infection progressed with the anterior chamber and cornea becoming increasingly infiltrated. His right eye eventually required enucleation (Images courtesy of Dr. Dean Eliott)

*Candida* endophthalmitis. Patients with more severe eye infection, which is commonly seen in *Aspergillus* endophthalmitis, usually have more significant vitritis. The inflammation may also extend to the aqueous, and white blood cells in the aqueous may settle out as a hypopyon. The presence of hypopyon is associated with worse visual acuity outcome [9]. Subretinal abscess is a rare finding encountered in severe fungal endophthalmitis and can occur in both *Aspergillus* and *Candida* endophthalmitis [40, 97]. It may also occur in bacterial endophthalmitis.

Both yeasts and molds have been described as causes of fungal endophthalmitis (Fig. 13.1). *Aspergillus* endophthalmitis is the most common type of mold endophthalmitis in patients with hematologic malignancies or after HSCT transplantation [94], and 23 % of endogenous *Aspergillus* endophthalmitis cases reported in the literature 1949–2001 occurred in solid organ transplant recipients [78]. *Aspergillus* endophthalmitis is underdiagnosed during life, especially if patients are in the intensive care setting and under sedation. In an autopsy of 85 liver transplant patients, of the 6 patients who were found to have *Aspergillus* endophthalmitis, only one was diagnosed before death [36]. The eye was the second most common site of infection in this series, after the lungs. Involvement of the retina and choroid, including retinal and choroidal vessels, may be a prominent feature of *Aspergillus* endophthalmitis. In a pathology study of enucleated or autopsy eyes that included 13 cases of endogenous Aspergillus endophthalmitis (four in organ transplant recipients), retinal or choroidal involvement was noted in 62 % and in all cases, the fungi were noted primarily within the subretinal space [75]. At sites of heaviest infiltration, the choroid, retinal pigment epithelium, and retina were necrotic. The first symptom of endogenous mold endophthalmitis may be blurred vision, but in sedated, very ill patients unable to complain of eye symptoms, the eye findings that may prompt an ophthalmology consultation may be scleral hemorrhage or conjunctival inflammation

[94]. As mentioned in a prior section, the treatment for *Aspergillus* endophthalmitis often requires vitrectomy due to the severity of disease and is usually combined with intravitreal and systemic antifungal therapies. The prognosis for *Aspergillus* endophthalmitis in transplant patients is generally poor. In a review of 56 cases of mold endophthalmitis reported in the literature, 23 % had an improvement in vision after treatment, and this difference was not significantly different in the subset who had HSCT or hematologic malignancy [94]. Transplant patients with mold fungemia and endophthalmitis have a high mortality. Only 27 % of 15 patients (including eight with HSCT) with a hematologic malignancy and mold endophthalmitis survived beyond 4 weeks in one study from a cancer center [51].

*Candida* endophthalmitis appears to occur less often than *Aspergillus* endophthalmitis in transplant patients. It is usually associated with preceding candidemia [40, 62]. Endogenous *Fusarium* endophthalmitis has been reported in a HSCT recipient who had bilateral kidney infiltration by *Fusarium* [42], as well as in patients with hematologic malignancies some of whom have undergone HSCT [51]. *Scedosporium apiospermum* (the asexual form of *Pseudallescheria boydii*) and *S. prolificans* are relatively common causes of fungal endophthalmitis in transplant patients. The overall incidence of disseminated *Scedosporium* infection is 1 per 1000 transplant patients, and it is most common in lung transplant patients [11]. The prognosis for ocular involvement is universally poor. Moreover, mortality from disseminated *Scedosporium apiospermum* infection has been reported to be as high as 61 % despite antifungal therapy and almost 100 % in lung transplant patients [60]. It can be diagnostically challenging to differentiate *Scedosporium* from *Aspergillus*. Like *Aspergillus*, *Scedosporium* may also cause a severe vitritis and involve the macula [92]. On histopathology, *Scedosporium* cannot be distinguished from *Aspergillus* because both have septate hyphae with acute angle branching. However, the appearance of the two molds on culture is different. Treatment of *Scedosporium* is often difficult due to lack of clinical response to antifungal agents such as amphotericin; voriconazole may be the most effective agent.

Bacterial endogenous endophthalmitis is less common than fungal endophthalmitis in the transplant population. Case reports have included *Nocardia* endophthalmitis in a cardiac transplant patient [80] and in a renal transplant recipient [88], nontuberculous *Mycobacterium* endophthalmitis in a cardiac transplant patient [58], bilateral *Pseudomonas* endophthalmitis after lung transplantation [26], and *Listeria monocytogenes* endophthalmitis in a renal transplant patient [3]. The visual outcomes in these cases have been poor.

## 13.4 Endophthalmitis in Other Immunocompromised States

Patients receiving immunosuppressive medications for rheumatologic conditions, chemotherapy for cancer, or who have hematologic malignancies are at increased risk for endogenous endophthalmitis. Asplenic patients are at increased risk for invasive pneumococcal disease, and cases of pneumococcal endophthalmitis have been described.

### 13.4.1 Corticosteroids, Anti-TNFα Agents, and Endophthalmitis

Systemic glucocorticoids predispose patients to cataracts and glaucoma. Many patients on long-term glucocorticoid therapy require cataract or glaucoma surgery, which carries the risk of post-cataract or bleb-related endophthalmitis (see Chaps. 5 and 8). Whether or not they are at increased risk compared to the general population is unknown. Corticosteroid use is also prevalent in immunosuppressed patients who develop endogenous endophthalmitis. In a review of endogenous *Aspergillus* endophthalmitis cases, 43 % of patients had received corticosteroids before developing endophthalmitis, although some patients also had other predisposing medical conditions [78]. *Nocardia* endophthalmitis has been described in a number of patients receiving corticosteroids [34, 37, 47]. Anti-TNFα agents have been associated with bacterial endophthalmitis in patients with rheumatoid arthritis. The pathogens reported include gram-positive cocci and rods, gram-negative rods, and mycobacterial species [59, 87].

### 13.4.2 Patients with Hematologic Malignancies

Patients with hematologic malignancies can be immunocompromised from disease-related neutropenia or iatrogenically from chemotherapy. Both yeasts and molds cause serious invasive fungal infections in patients with leukemia, and the resultant fungemia predisposes them to endophthalmitis. There have been several reports of mold endophthalmitis, including *Fusarium* and *Scedosporium*, in patients with acute myeloblastic leukemia [14, 72, 77, 91]. *Aspergillus* endophthalmitis has been described in patients with acute lymphoblastic or chronic lymphocytic leukemia [21, 41, 55]. A report of 23 cases of fungal endophthalmitis at a cancer center found that 83 % occurred in patients with hematologic malignancies (most with leukemia), and all 15 of the mold endophthalmitis cases occurred in these patients [51]. The molds were *Fusarium* (five cases), Aspergillus (four), *Scedosporium* (four), and *Rhizomucor* or *Mucor* (two). Bacterial endophthalmitis can also develop in patients with hematologic malignancies [67, 96].

### 13.4.3 Asplenic Patients

Asplenic patients are predisposed to bacteremia with encapsulated organisms, especially *S. pneumoniae*. Several cases of exogenous and endogenous pneumococcal endophthalmitis in asplenic patients have been reported [13, 22, 32, 64]. Patients who are asplenic should receive pneumococcal vaccinations, which may prevent some of these infections.

## 13.5 Endophthalmitis in Patients with Diabetes Mellitus

Diabetes mellitus affects 9 % of the global adult population [100] and 12 % of US adults [12]. The incidence increases with age: diabetes is present in 4 % of adults in ages 20–44 years, 16 % in ages 45–64, and 26 % in ages ≥65 [12]. Diabetic patients are at increased risk of developing infections, primarily due to poor glycemic control, diabetic neuropathy, and impaired innate and adaptive immune responses [46]. They are more than twice as likely to be hospitalized for infection as nondiabetic patients [46]. Diabetic patients also may be at increased risk for ocular infections, partly due to altered tear film and decreased barrier function of the corneal epithelial basement membrane [27].

### *13.5.1 Exogenous Endophthalmitis*

Exogenous endophthalmitis most commonly occurs in this population after ocular surgery or intravitreal injection. Diabetic patients have a higher rate of ocular surgery than the general population due to an increased risk of cataract and need for surgery to address complications of diabetic retinopathy. However, diabetes does not appear to increase the risk of post-cataract surgery. The best data come from the prospective European multicenter trial of cataract surgery involving 16,603 patients [29]. In that trial, diabetes was present in 14 % of patients but was not a risk factor for developing endophthalmitis. A case-control study from Singapore found similar results [99]. Diabetic patients who develop post-cataract endophthalmitis may benefit from vitrectomy more than nondiabetic patients, however. Diabetic patients comprised 14 % of the 420 patients with post-cataract endophthalmitis in the Endophthalmitis Vitrectomy Study (EVS), and diabetics treated with initial vitrectomy had a better chance of visual recovery to 20/40 or better than did diabetics treated only with tap/biopsy (57 % vs. 40 %) [25]. This result was true even in the group who presented with better than light perception vision.

The visual outcome in diabetics with postoperative endophthalmitis appears to be worse than for nondiabetics, with fewer patients recovering vision better than 20/100 [25, 74]. In the EVS, only 39 % of diabetics compared with 55 % of nondiabetics achieved 20/40 final vision [25]. In addition, patients with diabetic retinopathy may be at increased risk for rapid retinopathy progression and a poorer visual outcome after endophthalmitis [24, 50].

### *13.5.2 Endogenous Endophthalmitis*

Diabetes is a common comorbid medical condition in endogenous endophthalmitis and is associated with both bacterial and fungal endophthalmitis (Fig. 13.2) [39, 52, 53, 105]. In a review of 342 cases of endogenous bacterial endophthalmitis reported

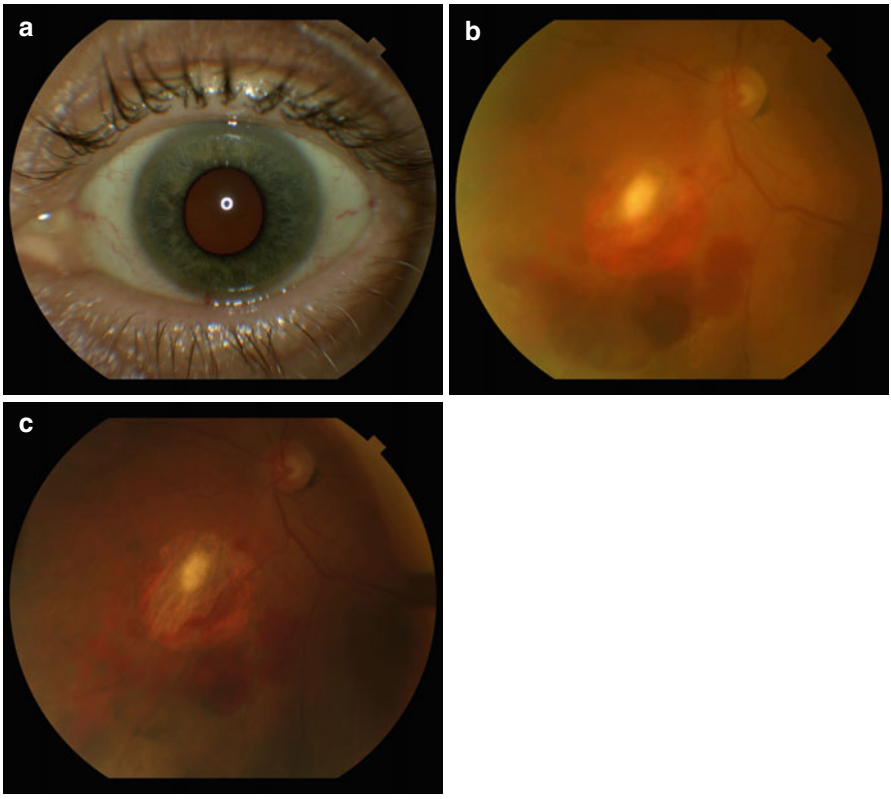


**Fig. 13.2** A 56-year-old man with insulin-dependent diabetes, end-stage alcoholic liver disease, and recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) skin abscesses was admitted for MRSA bacteremia and an epidural abscess. He presented with new floaters in the left eye. (**a**) His anterior chamber exam was unremarkable. (**b**) His fundus examination revealed vitritis and a retinochoroidal abscess surrounded by hemorrhage. The patient had a vitreous fluid removal which did not show any organisms on Gram stain or culture. He was treated with intravenous vancomycin and one injection of intravitreal vancomycin. His epidural abscess was drained. (**c**) Nine days after the intravitreal vancomycin injection, the vitritis, hemorrhage, and retinochoroidal abscess had decreased significantly in size (Images courtesy of Dr. Dean Eliott)

in the literature, 1986–2012, 33 % of patients had diabetes, 5 % IVDU, 3 % HIV, 3 % malignancy, and 3 % autoimmune diseases [39]. Animal models have demonstrated increased blood-ocular barrier permeability as a part of general increase in vascular permeability caused by diabetes, facilitating the development of endogenous endophthalmitis [17].

Among the East Asian population, diabetes is a significant risk factor for *Klebsiella pneumoniae* liver abscess and endogenous endophthalmitis [16, 82, 98]. A review of 602 patients with *Klebsiella* liver abscess treated in southern Taiwan over a 20-year period identified endophthalmitis in 7 % [82]. Diabetes was a significant risk factor for developing endophthalmitis: 79 % of the endophthalmitis cohort had diabetes

versus 55 % of the non-endophthalmitis cohort. Diabetes was also associated with a worse visual outcome in patients who had endophthalmitis. On examination, endogenous *Klebsiella* endophthalmitis may produce marked vitreous inflammation with a relatively quiet anterior segment [89]. Early diagnosis and intravitreal antibiotic treatment may salvage useful vision, although outcomes are generally poor.

In other parts of the world, endogenous bacterial endophthalmitis is more heterogeneous in etiology among diabetic patients. Gram-positive bacteria are the most common pathogens, and endocarditis, osteomyelitis, cellulitis and other soft tissue infections, and pneumonia are commonly reported sources of bacteremia [2, 10, 102, 104]. Gram-negative pathogens have also been reported, including *Citrobacter* [20], *E. coli* [68], and *Serratia* [28]. Treatment of endogenous endophthalmitis is discussed in Chap. 10.

Fungal endogenous endophthalmitis occurs in diabetic patients, with *Candida* endophthalmitis more common than *Aspergillus*. The treatment is the same as for nondiabetic patients (see Chap. 10).

## 13.6 Conclusion

Endophthalmitis in immunocompromised patients has a different differential diagnosis depending on the underlying cause of immunocompromise. Endogenous endophthalmitis is more common in immunocompromised patients than in immunocompetent patients. Prompt diagnosis and treatment are essential for preserving vision.

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# Chapter 14
# Antibiotic Resistance in Endophthalmitis Pathogens

**Paulo J.M. Bispo, Elizabeth M. Selleck, and Michael S. Gilmore**

## 14.1 Introduction

Resistance to antimicrobial agents used to treat human infections is one of the major public health threats of the twenty-first century [1]. Many have warned of the prospect of a post-antibiotic era [2–4] as several multidrug-resistant pathogens have emerged as serious threats [5]. Among these common and increasingly resistant pathogens are methicillin-resistant *Staphylococcus aureus* (MRSA), antibiotic-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus*, and multidrug-resistant *Pseudomonas aeruginosa*. MRSA causes about 80,000 severe infections per year and 11,000 deaths [5] and has become an increasingly common cause of ocular infections [6–10]. Although MRSA is a leading cause of hospital-associated infections, some strains (such as USA300 strain) have successfully disseminated into community settings [11] and may be more virulent than hospital-adapted strains [12].

Although organisms that cause most ocular infections originate from the patient's own microbiota, increasing use of antimicrobial agents for treatment and prophylaxis has resulted in an increase in resistant organisms isolated from ocular infections [14, 15]. In the era of molecular microbiology and genomics, we have learned much about the mechanisms that bacteria use to circumvent the lethal activity of antibiotics and how specific antibiotic-resistant lineages emerge in a specific niche. We also have an increased understanding of the pharmacokinetic properties of antibiotics in ocular tissues. In this chapter, we review the occurrence of antibiotic resistance among microbes that cause endophthalmitis.

P.J.M. Bispo, PhD • E.M. Selleck, PhD • M.S. Gilmore, PhD (✉)
Department of Ophthalmology, and Department of Microbiology and Immunology, Harvard Medical School, Boston, MA, USA

Department of Ophthalmology, Massachusetts Eye and Ear, Boston, MA, USA
e-mail: Michael_Gilmore@meei.harvard.edu



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## 14.2 Etiology of Antibiotic Resistance

Antimicrobial resistance is an inevitable consequence of the broad use of antibiotics in medicine, veterinary care, and agriculture. The use of antibiotics promotes the success of organisms possessing mechanisms for resistance, including those conveyed by mobile elements that can be exchanged among human pathogens.

Many of the genes encoding resistance are ancient. In a study of ancient DNA from 30,000-year-old permafrost (Late Pleistocene), D'Costa and colleagues identified a highly diverse collection of genes encoding resistance to beta-lactam, tetracycline, and glycopeptide antibiotics [13]. However, the selection and spread of these resistance elements among pathogens that cause human or animal infections are a relatively new event that followed the introduction of the antibiotics into the clinical practice in the mid-1940s. Moreover, exposure to some antibiotics selects for the outgrowth of spontaneous mutants, where mutations in DNA alter the amino acid sequence and structure of the protein targeted by the antibiotic.

## 14.3 Methods for Antimicrobial Susceptibility Testing

Resistance to antibiotics is routinely detected in vitro by using a combination of qualitative and quantitative susceptibility testing methods. The most common method used in the daily routine of clinical microbiology laboratories has been the disk diffusion method, which allows the categorization of the most important clinical bacterial pathogens as susceptible, intermediate, or resistant to a panel of different antibiotics. The test is based on the use of commercially available filter paper disks impregnated with antibiotic, which is applied to the surface of an agar plate that has been inoculated with the test bacteria. The antimicrobial molecule diffuses through the agar and creates a gradient of concentration surrounding the disk, with higher concentrations of drug near to the disk and lower as the distance from the disk increases. As the inoculated bacterial lawn grows, there will be a clear zone of inhibition around the disks in the areas where the concentration of the drug is inhibitory, which is influenced by the gradient of drug diffusion (Fig. 14.1a). The diameter of this inhibition zone is measured and a category is assigned according to defined interpretative criteria.

Dilution methods performed either on agar or broth medium are used to determine the minimal inhibitory concentration (MIC) of an antibiotic against a test isolate. The broth dilution can be performed in tubes with a volume higher than 1 mL (macrodilution) or in microplates having from 0.1 to 0.2 mL of liquid medium containing the antimicrobial agent serially diluted (at $\log_2$). The tube or well in the microplate containing the lowest concentration of antibiotic that inhibits visible bacterial growth is defined as the MIC (Fig. 14.1b, c). The microdilution plates can be visually inspected or read by a plate reader, which facilitates the analysis of multiple plates tested in the routine. A similar approach is the basis for the susceptibility

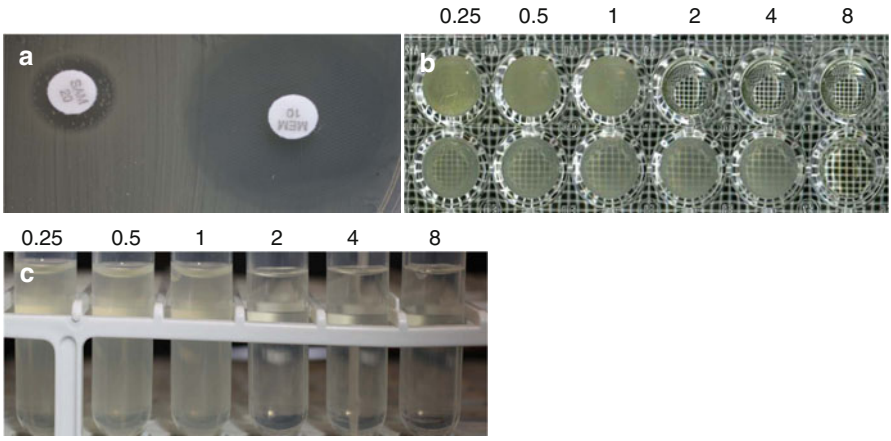


**Fig. 14.1** (**a**) An example of the disk diffusion method. A solution of *Escherichia coli* at 0.5 McFarland standard was prepared in sterile saline and inoculated on Mueller-Hinton agar. Disks of ampicillin-sulbactam (*SAM*) and meropenem (*MEM*) were applied on the agar surface. After incubation for 18 h at 37 °C, the isolate showed to be resistant to ampicillin-sulbactam (zone diameter of 8 mm) and contained a subpopulation growing in the small inhibition zone close to the disk. The isolate was susceptible to meropenem (zone diameter of 24 mm). (**b**) Broth microdilution test of oxacillin against two *S. aureus* isolates. *Upper lane* shows an isolate that was able to grow up to 1 μg/mL of oxacillin and thus the MIC is equal to 2 μg/mL (susceptible) and *bottom lane* an isolate that was inhibited by 8 μg/mL of oxacillin (resistant). (**c**) Broth macrodilution test of oxacillin using the susceptible *S. aureus* isolate as shown in panel **b**. Numbers above the microplate wells and tubes correspond to the antibiotic concentrations in μg/mL

testing employed by automated methods, which is frequently used in clinical laboratories since it combines species identification and antibiogram and can deliver faster results. Finally, most recent PCR-based technologies may detect the genes that are associated with important resistance phenotypes such as *mec*A, *van*A and *van*B, and beta-lactamases that are widely disseminated among gram-negative organisms.

## 14.4 Causative Pathogens and Antimicrobial Prophylaxis

The ocular surface of healthy individuals is colonized by gram-positive organisms, with coagulase-negative staphylococci as the most common organism in healthy conjunctiva, lids, and tears, followed by *Propionibacterium acnes*, *Corynebacterium* species, and *S. aureus* [16, 17]. Less frequently, other gram-positive organisms such as *Enterococcus* species, *S. pneumoniae*, viridans group streptococci, *Bacillus* species, gram-negative rods, and fungi are also isolated from the ocular surface microbiota [16, 17]. Organisms that colonize the ocular surface can access the aqueous and vitreous following eye surgery, intravitreal injections, and penetrating globe injury [18]. For this reason, gram-positive organisms originating from the patient's

conjunctiva and eyelid microbiota, such as coagulase-negative staphylococci (most commonly *S. epidermidis*), are the main causes of exogenous endophthalmitis [19–22]. This is supported by data in the Endophthalmitis Vitrectomy Study, which showed that 67.7 % of paired coagulase-negative staphylococcal isolates from the eyelid and intraocular fluids were indistinguishable by pulsed-field gel electrophoresis [23]. Although the overall incidence of endophthalmitis is relatively low, a substantial number of patients are affected by this sight-threatening infection given the large and increasing number of intraocular procedures performed annually. Some of these infections are caused by organisms resistant to antimicrobial agents used for prophylaxis and treatment [24, 25]. For example, cataract surgery represents the most frequent surgical procedure performed by ophthalmologists, with two to three million surgeries performed each year in the United States [26, 26A]. Additionally, there has been a large increase in the number of intravitreal injections performed for the treatment of a range of retinal diseases [27]. Development of acute-onset endophthalmitis is the leading blinding complication of such procedures, with incidences ranging from 0.01 to 0.2 % following cataract surgery and 0.006–0.16 % following intravitreal injection [28].

Patients are commonly prescribed topical antibiotics for prophylaxis of associated infections following these procedures that aim to sterilize the ocular surface and achieve therapeutic concentrations in the anterior chamber. Because of this, the use of topical antibiotics has paralleled the increase in the number of ocular surgeries and other intraocular procedures, which has resulted in the emergence of antibiotic-resistant organisms as significant causes of postoperative ocular infections [25]. In addition to topical application, subconjunctival or retrobulbar injection of antibiotics including vancomycin or gentamicin and intracameral use of cefuroxime or moxifloxacin have been used at some centers for perioperative prophylaxis of endophthalmitis [29, 29A]. However, there has been only one prospective randomized trial evaluating the efficacy of perioperative antibiotic prophylaxis and that was for intracameral cefuroxime [29B]. Perioperative prophylaxis of endophthalmitis is discussed further in Chap. 15.

Despite the controversy surrounding the efficacy of prophylactic antibiotics in preventing postoperative endophthalmitis, the use of prophylactic antibiotics, particularly topical fluoroquinolones, is a very common practice among ophthalmologists. In a 2007 survey of the members of the American Society of Cataract and Refractive Surgery, 91 % of surgeons prescribe topical antibiotics at the time of cataract surgery, 88 % prescribe topical antibiotics for 1–3 days preoperatively, and nearly all surgeons (98 %) prescribe topical antibiotics for at least 1 week postoperatively [30]. Fluoroquinolones were the preferred antibiotics for topical use among 93 % of the surgeons, with gatifloxacin and moxifloxacin of the 8-methoxyfluoroquinolone group being the most common antibiotics prescribed. This preference is due to the wide spectrum of activity of fluoroquinolones against gram-positive and gram-negative pathogens, with the 8-methoxyfluoroquinolones demonstrating increased potency against gram-positive organisms and reduced rates of resistance compared to older fluoroquinolones such as ciprofloxacin, ofloxacin, and levofloxacin [31]. As expected, the widespread use of prophylactic topical fluoroquinolones

has been associated with the selection of spontaneous resistant mutants in the ocular surface microbiota [32–35]. This has paralleled the increasing resistance to fluoroquinolones among staphylococcal isolates in endophthalmitis [14, 15, 36].

Although topical fluoroquinolones are widely used for prophylaxis of postoperative and post-injection endophthalmitis, in vitro susceptibility data demonstrate that these antibiotics do not have the best coverage against commensal bacteria isolated from the conjunctiva of patients undergoing anterior segment surgery [16, 37–40] or intravitreal injections [41, 42] (Table 14.1). The antibiotics with the highest in vitro rates of susceptibility against commensal coagulase-negative staphylococci and *S. aureus* are vancomycin (100 %), tetracycline (from 80 to 100 %), and trimethoprim-sulfamethoxazole (from 74 to 100 %) (Table 14.1). While there is a noted geographic difference in the susceptibility of commensal isolates to fluoroquinolones, studies that collected isolates more recently (from 2007 to 2009) found lower rates of susceptibility to the fluoroquinolones (63 % for ciprofloxacin and levofloxacin and 78 % to newer fluoroquinolones) than older isolates. This suggests that emerging resistance to fluoroquinolones increases with time, paralleling an increase in the use of these antibiotics, and may account for the differences seen between studies evaluating the susceptibility of ocular commensal organisms [16, 37–42]. Resistance to macrolides, another class of antibiotics that are commonly used in ophthalmology, is also frequent for commensal isolates with erythromycin susceptibility ranging from 29 to 80 % for *S. aureus* and from 37 to 49 % for coagulase-negative staphylococci (Table 14.1).

In addition to the high baseline level of fluoroquinolone and macrolide resistance in bacteria colonizing the conjunctiva, exposure to topical antibiotics is associated with the emergence of resistant isolates (Table 14.2). Various antibiotic regimens have been evaluated for an association with selection of resistant organisms. In patients undergoing cataract surgery, topical levofloxacin prophylaxis beginning one week preoperatively and continuing for two weeks postoperatively has been associated with a high frequency of resistant commensal *S. epidermidis* [34]. These isolates harbor multiple mutations in the quinolone resistance-determining region of the topoisomerase subunits GyrAB (DNA gyrase) and ParCE (topoisomerase IV). Isolates carrying these mutations and selected after exposure to levofloxacin demonstrated decreased in vitro susceptibility compared to isolates recovered before antibiotic exposure. These isolates were also more resistant to ofloxacin, norfloxacin, gatifloxacin, and moxifloxacin. This cross-resistance between different fluoroquinolones may be due to the fact that isolates selected after use of levofloxacin contain double point mutations in DNA gyrase and topoisomerase IV. Of note, in the same study, in the group of eyes receiving gatifloxacin 0.3 %, there was no correlation between its topical application and isolation of resistant *S. epidermidis* mutants [34].

With the increasing frequency of intravitreal injections for treatment of age-related macular degeneration, diabetic retinopathy, and retinal vein occlusions, a debate has continued on the need to apply topical antibiotics for prophylaxis of post-injection endophthalmitis [43, 44]. Monthly use of anti-vascular endothelial growth factor (anti-VEGF) is accompanied by repeated use of topical antibiotics,

**Table 14.1** Antimicrobial susceptibility profile of commensal coagulase-negative staphylococci and *S. aureus* isolates from the conjunctiva of patients undergoing cataract surgery or intravitreal injection

| Organism | Intraocular procedure | Year of sampling | Location | No. of isolates tested | % of susceptible isolates to: | | | | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | OXA/CEF | ERY | TMP/SMZ | TET | VAN | CIP | LEV | MOX | GAT | |
| CoNS | IV injection | 2009 | Tennessee, USA | 27 | 74 | 37 | 74 | 100[a] | 100 | – | 52 | 63 | 67 | Kim et al. [41] |
| | IV injection | 2008–2009 | California, USA[b] | 59 | 50 | | | ≥85 | 100 | 58 | 61 | 69 | 69 | Moss et al. [42] |
| | Cataract surgery | 2007–2009 | Missouri, USA | 127 | 54 | 49 | 83 | 91 | 100 | 63 | 63 | 75 | 78 | Hsu et al. [39] |
| | Not described | 2007 | Japan[b] | 58 | 62 | – | – | – | – | – | 60 | 60 | 60 | Hori et al. [38] |
| | Cataract surgery | 2006–2007 | Spain[b] | 707 | 51 | 44 | 89 | 80 | 100 | 74 | 83 | – | – | Fernandez-Rubio et al. [16] |
| | Cataract surgery | 2006 | South Korea | 263 | – | – | – | – | – | 69 | 78 | 90 | 91 | Park et al. [40] |
| | Cataract surgery | 2004 | Brazil | 38 | 76 | – | – | – | 100 | 89 | – | – | 100 | Arantes et al. [37] |
| *S. aureus* | Cataract surgery | 2007–2009 | Missouri, USA | 11 | 36 | 29 | 100 | 82 | 100 | 45 | 56 | 43 | 50 | Hsu et al. [39] |
| | Not described | 2007 | Japan | 10 | 62 | – | – | – | – | – | 60 | 60 | 60 | Hori et al. [38] |
| | Cataract surgery | 2006–2007 | Spain[b] | 196 | 86 | 80 | 98 | 93 | 100 | 85 | 88 | – | – | Fernandez-Rubio et al. [16] |

*CoNS* coagulase-negative staphylococci (some reports specified *S. epidermidis*), *IV* intravitreal, *OXA*/CEF oxacillin/cefoxitin, *ERY* erythromycin, *TMP/SMZ* trimethoprim-sulfamethoxazole, *TET* tetracycline, *VAN* vancomycin, *CIP* ciprofloxacin, *LEV* levofloxacin, *MOX* moxifloxacin, *GAT* gatifloxacin

[a]Doxycycline was tested.

[b]Frequencies (%) are approximate values. Percentage of susceptible isolates was inferred by subtracting the frequency of resistant isolates reported in the original paper and may be mixed with small % of isolates with intermediate susceptibility.

**Table 14.2** Association between antibiotic prophylaxis for prevention of endophthalmitis and selection of resistant bacteria at the ocular surface microbiota

| Reference | Baseline eye disease | Treatment | Number of intravitreal injections followed by antibiotic prophylaxis | Topical antibiotic (no. of patients) | Number of patients per group | | Topical antibiotic regimen | Non-susceptibility rates[a] in the control group or before topical instillation of antibiotic | Non-susceptibility rates[a] following exposure[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Study | Control | | | |
| Miyanaga et al. [34] | Cataract | Cataract surgery | – | Gatifloxacin (79) and levofloxacin (73) | 152 | None[c] | QID 1 week before and TID for 2 weeks after surgery | 40 % GAT, LEV, and OFL; 26.7 % MOX[d] | 86.7 % GAT, LEV, and OFL; 73.3 % MOX[d] |
| Kim and Toma [32] | AMD and others[e] | Bevacizumab or ranibizumab IVI | 3–12 in 1 year | Fluoroquinolones[f] (6 to each antibiotic) | 24 | 24 (fellow eye) | Repeated use for up to 1 year | 58.6 % AZI; 59.4 % OFL; 56.1 % LEV; 19.7 % GAT; 25.6 % MOX | 95 % AZI; 82 % OFL; 79 % LEV; 42 % GAT; 65 % MOX |
| Milder et al. [33] | AMD | Bevacizumab or ranibizumab IVI | At least 3 (average 7) | Fluoroquinolone[g] (11) or polymyxin-trimethoprim (29) | 40 | 40 (fellow eye) | QID for 4 days following injection | 25 % GAT/MOX. 27.7 % TMP | 87.5 % GAT/MOX; 28.6 % TMP |

(continued)

**Table 14.2** (continued)

| Reference | Baseline eye disease | Treatment | Number of intravitreal injections followed by antibiotic prophylaxis | Topical antibiotic (no. of patients) | Number of patients per group | | Topical antibiotic regimen | Non-susceptibility rates[a] in the control group or before topical instillation of antibiotic | Non-susceptibility rates[a] following exposure[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Study | Control | | | |
| Yin et al. [35] | AMD | Ranibizumab IVI | At least 3 | Moxifloxacin | 84 | 94 | QID for 3 days following injection | 7.7 % MOX | 50 % MOX |

*AMD* age-related macular degeneration, *CNV* choroidal neovascularization, *IVI* intravitreal injection, *AZI* azithromycin, *LEV* levofloxacin, *OFL* ofloxacin, *MOX* moxifloxacin, *GAT* gatifloxacin, *TMP* trimethoprim, *QID* 4× daily, *TID*, 3× daily

[a]Rates of resistance among commensal isolates of staphylococci (mostly coagulase-negative staphylococci)

[b]Resistance rates at the last visit for each study

[c]Rates of resistance and emergence of resistant mutants for each group was compared between isolates recovered before instillation of topical antibiotics (baseline) and after 3 weeks of continuous use of gatifloxacin or levofloxacin.

[d]Non-susceptibility rates before and after the instillation of levofloxacin are shown. The gatifloxacin group was omitted as it was not different comparing before and after treatment.

[e]Most of the patients included had AMD. Others include patients with choroidal neovascularization secondary to myopic degeneration ($n=2$) and ocular histoplasmosis ($n=1$) and of idiopathic cause ($n=1$).

[f]Either ofloxacin 0.3 %, gatifloxacin 0.3 %, moxifloxacin 0.5 %, or azithromycin 1 %

[g]Either ofloxacin 0.3 % or moxifloxacin 0.5 %

which has allowed for the assessment on the longitudinal impact of antimicrobial exposure in the selection of multidrug-resistant organisms colonizing the conjunctiva. In a series of longitudinal studies on the impact of antibiotic use in the emergence of resistant commensal organisms, it was shown that the repeated use of topical fluoroquinolones and azithromycin was associated with a significant increase in the isolation of resistant bacteria, especially *S. epidermidis*, in the conjunctiva microbiota [32, 41, 45]. High rates of resistance were seen following exposure especially for ofloxacin and levofloxacin (82 % and 79 %, respectively) and azithromycin (95 %). Rates of resistance to gatifloxacin (42 %) and moxifloxacin (65 %) were also increased compared to the baseline in patients receiving topical fluoroquinolones [32]. Similarly, in an independent study including 84 patients newly diagnosed with age-related macular degeneration (i.e., with no history of intravitreal injection) and 94 controls, the topical application of moxifloxacin four times daily for three days following the injection of ranibizumab was associated with a significant increase in the resistance rates to moxifloxacin compared to control eyes receiving no antimicrobial prophylaxis, especially among coagulase-negative staphylococci [35]. Cultures and susceptibility testing showed resistance rates to moxifloxacin increased from 0 % at baseline to 30 % in the first month, 11 % in the second month, and 50 % in the third month at final follow-up. Resistance rates in the control group were 11 % at baseline and remained below 8 % at each evaluation during the three months of study [35].

While antibiotic resistance is seen in the commensal microbiota after exposure to fluoroquinolones and macrolides, this might not be the case for other antimicrobial classes. For patients with unilateral exudative macular degeneration who had received post-injection topical antibiotic courses at least three times previously, topical use of either ofloxacin or moxifloxacin was associated with an increase in fluoroquinolone-resistant bacteria from 25 % in control to 88 % in study eyes [33]. Use of topical trimethoprim/polymyxin prophylaxis was not associated with a significant increase in resistance to trimethoprim (28 % resistance in control and study eyes).

Many retina specialists advocate against the use of topical antibiotic prophylaxis for intraocular injections because of the lack of evidence for efficacy and the demonstrated risk of selecting resistant bacteria [43, 44, 46, 47]. Application of povidone-iodine achieves adequate reduction of commensal ocular surface bacteria [48], has not been demonstrated to have impact in the selection of antibiotic-resistant organisms [49], and is therefore the preferred practice. Given the low incidence of post-injection endophthalmitis, it is difficult to perform randomized prospective studies to evaluate the efficacy of antibiotic prophylaxis. However, there is increasing evidence that the incidence of post-injection endophthalmitis remains low in eyes not receiving topical antibiotic prophylaxis [46, 50, 51] and that in some cases the use of topical antibiotics actually may be associated with a higher incidence of post-injection endophthalmitis [52, 53]. A recent retrospective case-control study found a higher incidence of endophthalmitis (0.05 % of 57,654 injections) in the group that used prophylactic topical antibiotics for 4 days post injection than in the group that used no post-injection antibiotics (0.03 % of 89,825 injections) [54]. In

this study, 40 % of the culture-positive endophthalmitis cases in the group that used topical antibiotics were due to bacteria resistant to the prescribed topical antibiotic, while none of the culture-positive cases were due to resistant bacteria in the no-antibiotic group. Although post-injection endophthalmitis may occur in the presence or absence of prophylactic antibiotics, the selection of resistant isolates during prophylaxis that may cause a subsequent infection should be of concern as it will make treatment with antibiotics more difficult. In addition, multidrug-resistant *S. epidermidis* endophthalmitis isolates, including ciprofloxacin-resistant isolates, may be enriched for the carriage of multiple biofilm-associated genes including *aap*, *bhp*, and *ica*AD when compared to the susceptible isolates that do not carry these genes [55]. Therefore, selection of resistant strains may be associated with co-selection of virulence markers that would increase the ability of the bacteria to attach to surfaces in the eye chambers or to the artificial intraocular lens placed during cataract surgery and may facilitate the development of a biofilm-associated and persistent infection.

Because of the differences in design and prophylactic regimens used in published studies, it is difficult to conclude which antibiotic regimen might lead to the lowest selection of resistant organisms. However, the message that we can take from those studies is that independent of regimen or choice of antibiotic, previous exposure to any topical fluoroquinolone agent is associated with a risk for selection and enrichment of resistant populations in the microbial community colonizing the human conjunctiva.

## 14.5 Antimicrobial Resistance in Endophthalmitis

Similar to other areas of clinical practice, antimicrobial resistance among bacterial isolates causing ocular infections is a growing concern. Nationwide multicenter surveillance studies monitoring the rates of antibiotic-resistant ocular bacterial isolates in the United States [6, 7, 9] found remarkably high resistance levels for infections acquired in a community setting. In the TRUST study (Tracking Resistance in the United States Today), 16.8 % of *S. aureus* ocular isolates collected from 2005 to 2006 were methicillin-resistant (MRSA), and these were highly resistant to fluoroquinolones (≥75 % resistant), azithromycin (90.9 % resistant), and tobramycin (63.6 % resistant) [6]. Approximately 22 % of *S. pneumoniae* isolates were resistant to azithromycin. In the larger surveillance program ARMOR (Antibiotic Resistance Monitoring in Ocular MicroRganisms), among isolates collected through the year 2009, 39 % of *S. aureus* and 53 % of coagulase-negative staphylococci were methicillin-resistant, and a high percentage of these staphylococci were also highly resistant to fluoroquinolones, azithromycin, and tobramycin [9]. Pneumococcal resistance to azithromycin (25 %) was also similar to the incidence reported in the TRUST study.

The correlation between antibiotic resistance and clinical outcomes in endophthalmitis has not been clearly determined. However, one study reported an association between methicillin and fluoroquinolone resistance and poorer visual

outcomes in patients with acute postoperative endophthalmitis caused by coagulase-negative staphylococci [56]. Another study found that endophthalmitis due to MRSA had a worse visual outcome than endophthalmitis due to methicillin-susceptible *S. aureus* [10].

### 14.5.1 Methicillin Resistance in S. aureus (MRSA) and Coagulase-Negative Staphylococci

Methicillin resistance is a key mechanism of resistance in staphylococci and is significantly associated with higher resistance rates to other non-beta-lactam antibiotics, contributing to the spread and persistence of multidrug-resistant strains in several settings. Resistance to methicillin in both *S. aureus* and coagulase-negative staphylococci is conferred by an altered penicillin-binding protein (PBP2a) with reduced affinity for beta-lactam antibiotics [57]. PBP2a is encoded by the *mec*A gene, which is carried in the mobile genetic element called the staphylococcal cassette chromosome *mec* (SCC*mec*) [58]. The rates of methicillin resistance among ocular staphylococci isolates are on the rise [7, 8, 59]. Methicillin-resistant *S. aureus* may account for approximately 40 % of *S. aureus* isolates causing endophthalmitis [10]. In the Endophthalmitis Vitrectomy Study of post-cataract endophthalmitis, which included isolates from 1990 to 1994, MRSA caused 1.9 % of culture-positive cases [20]. Rates of MRSA in serious ocular infections have increased in the United States from 29.5 % in 2000 to 41.6 % in 2005 [7]. In a retrospective study of culture-positive endophthalmitis cases treated at the New York Eye and Ear Infirmary from 1987 to 2011, the 109 *S. aureus* isolates showed a steadily increasing rate of methicillin resistance (MRSA), from 18 % in 1987–1991 to 55 % in 2007–2011 [59]. A similar increase in methicillin resistance was found for *S. epidermidis*. Because of the co-resistance to other antimicrobial classes, an increase in the rates of methicillin resistance among staphylococci may be accompanied by a rise in resistance to macrolides, lincosamides, and fluoroquinolones [6, 9]. Among MRSA isolates from endophthalmitis cases in one study, only 38 % were susceptible to gatifloxacin and moxifloxacin, 54 % to gentamicin, and 61 % to clindamycin, while almost all methicillin-sensitive *S. aureus* isolates were susceptible to the fluoroquinolones (95 %) and all were susceptible to gentamicin and clindamycin [10].

### 14.5.2 Fluoroquinolone Resistance

Topical fluoroquinolone agents (ciprofloxacin, ofloxacin, and levofloxacin) have been widely used for both prophylaxis and management of ocular infections. The 8-methoxyfluoroquinolones gatifloxacin (Zymar, Allergan) and moxifloxacin (Vigamox, Alcon) are widely used topical antibiotics due to their increased potency against gram-positive pathogens and reduced rates of resistance compared with the older fluoroquinolones [30, 31]. However, recovery of ocular

fluoroquinolone-resistant pathogens emerged soon after the introduction and widespread use of these agents in the 1990s, and resistance has significantly increased in the last two decades [25]. Both gatifloxacin and moxifloxacin simultaneously inactivate topoisomerases II (DNA gyrase) and IV, which are necessary for DNA replication. Older fluoroquinolones, including ciprofloxacin and levofloxacin, preferentially target either topoisomerase II or IV. Dual-acting fluoroquinolones not only demonstrate increased potency, but also are thought to minimize selection of resistant strains because of the double point mutations in both DNA gyrase and topoisomerase IV that are necessary for an organism to become resistant [31].

Although older fluoroquinolones are associated with higher resistance rates than the newer compounds, emerging resistance rates to gatifloxacin and moxifloxacin have been documented among coagulase-negative staphylococcal isolates from endophthalmitis cases [14, 15, 36]. Overall, fluoroquinolone susceptibility rates of gram-positive organisms from endophthalmitis cases vary according to geographic location and year of sampling and range from 51 to 92.3 % for ciprofloxacin and from 47 to 100 % for gatifloxacin and moxifloxacin [20–22, 59]. An increase in resistance has been documented in a series of studies assessing yearly fluoroquinolone resistance rates among coagulase-negative staphylococcal isolates recovered from endophthalmitis at the Bascom Palmer Eye Institute. Resistance rates ranged from 0 to 10 % for levofloxacin and ciprofloxacin from 1990 to 1994 and rose to nearly 60 % for both drugs from 2005 to 2011 [15, 36]. This growing resistance was also found for the 8-methoxyfluoroquinolones, with no resistant strains in the first period of sampling (1990–1994) but approximately 22 % in 1995–1999, 30 % in 2000–2004, and 60 % in 2005–2011 [15, 36]. Of interest, resistance to the newest 8-methoxyfluoroquinolone was detected to be emerging even among methicillin-susceptible *S. epidermidis* from patients with endophthalmitis following intraocular procedures. Prior exposure to the 8-methoxyfluoroquinolones was associated with the selection of *S. epidermidis* strains containing multiple mutations in the quinolone resistance-determining regions of *gyr*A and *par*C that resulted in low- and high-level resistance to these agents [14].

### *14.5.3 Vancomycin Resistance*

Vancomycin is currently the antibiotic of choice for intravitreal treatment of endophthalmitis due to gram-positive bacteria. Topical formulations may also be used for adjunctive therapy. Vancomycin is a glycopeptide antibiotic that binds to the D-Ala-D-Ala peptide termini of peptidoglycan precursors inhibiting cell wall synthesis in gram-positive organisms. Resistance to vancomycin may develop in clinically important bacteria such as *Enterococcus* species through the acquisition of *van* gene clusters, most commonly *van*A and *van*B, which synthesize the alternate peptide D-Ala-D-Lac to which glycopeptides bind with lower affinity [60]. While the transference of these genes to *S. aureus* has been already documented [61],

extensive dissemination of vancomycin-resistant *S. aureus* strains has not yet occurred, and isolation of strains carrying these genes is rare. However, reduced vancomycin susceptibility in *S. aureus*, including vancomycin-intermediate (VISA) and heterogeneous vancomycin-intermediate (hVISA) resistance, has become an increasing clinical problem in non-ocular infections and is due to modifications in the cell wall metabolism that result in thickening of the peptidoglycan layer [62]. To date, there is no report using reliable methods to detect and confirm these phenotypes in *S. aureus* isolated from endophthalmitis.

Enterococcal endophthalmitis is infrequent but may occur after ocular surgery and trauma or have an endogenous origin. These infections are associated with poor visual outcomes. *E. faecalis* is the most commonly isolated species as seen in a retrospective case series from different countries [63–65]. Rates of resistance to vancomycin are low (0–3.8 %) and to ciprofloxacin range from 15 to 30 %. Case reports of vancomycin-resistant *Enterococcus* have been described from patients in the United States, India, Canada, Mexico, and Taiwan. Most of these cases were caused by *E. faecium*. Only one case was caused by *E. faecalis* [66] and one by *E. gallinarum* [67], the latter being associated with a trauma caused while the patient was working on farm machinery. The *E. faecalis* case was a late-onset bleb-associated infection that developed 20 years after filtering bleb surgery [66]. The vancomycin-resistant *E. faecium* (VRE) endophthalmitis cases reported include one endogenous endophthalmitis case secondary to bacteremia in an immunocompromised patient [68], three postoperative cases including two following penetrating keratoplasty [69, 70], and one after cataract surgery [71].

### *14.5.4 Endophthalmitis Caused by Multidrug-Resistant Gram-Negative Bacteria*

Although very rare, clusters of endophthalmitis cases have occurred following inadvertent use during surgery of contaminated infusion fluids or surgical equipment. *Pseudomonas aeruginosa*, an organism that is rarely involved in endophthalmitis cases following uneventful cataract surgery, is one of the main causes of outbreaks of post-cataract surgery endophthalmitis, usually due to environmental contamination including the internal tubes of phacoemulsification machines and contaminated solutions used during the surgery [72]. *P. aeruginosa* endophthalmitis is usually associated with rapid progression, poor clinical outcomes, and high rates of enucleation [73]. Complicating these infections are the high rates of multidrug resistance among *P. aeruginosa*. In a series of endophthalmitis cases from India, authors identified 42 patients who developed infections caused by multidrug-resistant bacteria between the years of 2000 to 2007 [74]. Multidrug-resistant isolates were commonly gram-negative rods, mainly *Pseudomonas* species. Other species were identified less frequently, including *Burkholderia cepacia*, *Escherichia coli*, *Klebsiella pneumoniae*, *and Vibrio* species. Most of these patients had poor visual outcomes [74].

In an outbreak of post-cataract surgery endophthalmitis in Greece, *P. aeruginosa* isolates from 12 cases were resistant to aminoglycosides, quinolones, and piperacillin-tazobactam but susceptible to carbapenems and colistin (susceptibility to ceftazidime was not tested) [75]. In an outbreak of *P. aeruginosa* endophthalmitis involving 20 patients at a center in India, the source was in a contaminated operating room air conditioning system, and all isolates were resistant to multiple antibiotics and susceptible to colistin (susceptibility to other *Pseudomonas*-active antibiotics was not tested). Most of the patients were treated with intravitreal amikacin and cefazolin (both resistant in vitro) but did poorly, with 9 eyes requiring evisceration [76]. Several fulminant endophthalmitis cases caused by multidrug-resistant *P. aeruginosa* following keratoplasty were determined to be transmitted from donor tissue, as shown by pulsed-field gel electrophoresis [77]; outcomes were poor in these cases as well. Outbreaks due to susceptible *Pseudomonas* isolates have also occurred; one involving 45 cases occurred in a center in Brazil [77A]. It is important to determine the susceptibility profile of pathogens in endophthalmitis cases as soon as possible, since timely treatment with effective intravitreal antibiotics offers the best hope for recovering vision.

## 14.6 Pharmacokinetic and Pharmacodynamic Parameters as Predictors of Antimicrobial Efficacy

As discussed above, topical application of antibiotics for prophylaxis of endophthalmitis following intraocular procedures is a practice that has been reconsidered among ophthalmologists. In addition to the lack of evidence for efficacy in preventing endophthalmitis and the proven association with selection of antibiotic-resistant commensal organisms, topical antibiotics may not achieve therapeutic levels in the anterior chamber [78, 79].

Associating the in vitro activity and potency of particular antimicrobial agents with their pharmacokinetic profile (absorption, distribution, metabolism, and excretion) determines if appropriate concentrations are achieved in different tissues. These parameters may predict treatment efficiency and the likelihood of the selection of resistant mutants can be calculated. On the basis of these pharmacokinetic-pharmacodynamic (PK/PD) parameters, antimicrobial agents can be categorized into three common PK/PD categories. These include [1] the duration of time the concentration of antibiotic remains above the minimum inhibitory concentration (MIC) (T > MIC) [2], the ratio of the maximum concentration of the antibiotic in a specific tissue ($C_{max}$) to the MIC ($C_{max}$:MIC), and [3] the ratio of the area under the concentration-time curve at 24 h to the MIC ($AUC_{0\text{-}24}$:MIC). Which parameter predicts clinical and microbiological efficacy for a particular antibiotic depends on the mechanism of bactericidal activity for that antibiotic, which can be time- or concentration-dependent. Beta-lactams are examples of time-dependent antibiotics, so microbial killing depends on the time that the antibiotic concentration exceeds the MIC. Concentration-dependent antibiotics include the fluoroquinolones,

aminoglycosides, and macrolides. For these agents, bactericidal activity increases with the antibiotic concentration, so the primary determinant of efficacy is the level of antibiotic that can be achieved in the tissue [80, 81].

Penetration into the anterior chamber is different for each topical fluoroquinolone, with moxifloxacin 0.5 % showing the highest concentration followed by gatifloxacin and then besifloxacin [82]. This information has encouraged the use of fluoroquinolones with more tissue penetration for prophylaxis of endophthalmitis following surgeries [83, 84]. This decision is based in the logical thinking that the higher the antibiotic concentration in the anterior chamber, the better the efficacy in preventing infection. Attaining high intraocular concentrations is believed to be important in the days following sutureless surgeries, when there is a risk of contamination of the anterior chamber due to an influx of tears during postoperative hypotony or eye squeezing [85]. However, no randomized controlled trial has evaluated the efficacy of topical antibiotic prophylaxis given postoperatively for several days, as is commonly done after cataract surgery. A large multicenter randomized controlled trial of topical levofloxacin given immediately before and after cataract surgery found no prophylactic benefit [85A]. That study did not try to evaluate the use of several days of postoperative topical antibiotics, since all patients were given topical levofloxacin for 6 days beginning the day after surgery.

Only considering the maximum concentration that an antibiotic can achieve in the anterior chamber as a predictor of efficient microbial elimination leaves one important side of the equation out, namely, the minimum concentration of the antibiotic that is bactericidal to the pathogens causing endophthalmitis. In fact, using PK/PD parameters measured to predict efficacy against ocular staphylococcal isolates demonstrated that it is unlikely that any of the fluoroquinolones, even those with the best intraocular penetration, would be effective in eliminating resistant (as would be expected) or susceptible strains of *S. aureus* and coagulase-negative staphylococci from the anterior chamber [78, 79].

Categorization of bacteria as susceptible, intermediate, or resistant to a particular antibiotic is currently performed following breakpoints published by standard-setting groups such as the Clinical and Laboratory Standards Institute (CLSI) [86] and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [87]. These breakpoints are defined using multiple factors but are designed for antibiotic concentrations that can be achieved in the serum following systemic administration. It is difficult to determine the value and clinical impact of applying breakpoints established for systemic antibiotic use in the treatment of ocular infections using topical antibiotics. Of course, for isolates that carry mechanisms conferring high-level resistance to a particular antibiotic, the likelihood of achieving effective treatment will be minimal, regardless of whether differences exist between the systemic and local (topical) pharmacokinetics. However, even for isolates that are considered susceptible or low-level resistant by using the current systemic breakpoints, it is difficult to predict the successful microbial elimination or therapeutic efficacy using a topical regimen for each eye compartment. None of the newer fluoroquinolones (besifloxacin, moxifloxacin, and gatifloxacin) can achieve concentrations in the aqueous after a single topical instillation that would approach the MIC of ocular

*S. epidermidis* and *S. aureus* isolates either susceptible or resistant to ciprofloxacin [78]. Repeated doses may increase the mean aqueous humor concentration of the same antibiotics in patients undergoing cataract surgery, but repeated doses still do not provide concentrations that would be needed to achieve efficient microbial elimination [83, 84].

It is important to note that the attainable mean aqueous humor concentrations of besifloxacin, moxifloxacin, and gatifloxacin may also not be high enough to achieve efficient bactericidal activity even for fluoroquinolone-susceptible ocular isolates of *S. aureus* and *S. epidermidis*. For concentration-dependent antibiotics, including fluoroquinolones, PK/PD-based targets have been established that would predict the maximum efficacy and most favorable outcomes for systemic use. These include a $C_{max}$:$MIC_{90}$ ratio equal or higher than 10 and an $AUC_{0\text{-}24}$:$MIC_{90}$ ratio of 30–50 for gram-positive organisms [82]. The $C_{max}$:$MIC_{90}$ ratio values calculated for fluoroquinolone-susceptible ocular isolates of *S. aureus* and *S. epidermidis* are reported to be under the targeted value, 5.3 for moxifloxacin, 2.2 for besifloxacin, and 0.5 for gatifloxacin [78]. For ciprofloxacin-resistant and methicillin-resistant *S. aureus* and *S. epidermidis*, the $C_{max}$:$MIC_{90}$ ratios are below 0.03 for all the fluoroquinolones. This has been independently confirmed for moxifloxacin and gatifloxacin, which achieved $C_{max}$:$MIC_{90}$ ratios of 0.05 and 0.02, respectively, using the MIC values for a relatively large collection of coagulase-negative staphylococci ($n = 59$) isolated from endophthalmitis cases from 1993 to 2006 in South Florida [79].

As demonstrated above, none of the currently used topical fluoroquinolones are likely to be effective in eliminating microbial contaminants in the anterior chamber following surgery. Since the effectiveness of fluoroquinolones is concentration-dependent, a therapeutic goal to achieve better bactericidal activity would be to maximize exposure by increasing the aqueous humor concentration. In this scenario, different ways to deliver the antibiotic to the intraocular chamber to attain and maintain high concentrations in these compartments would be necessary to effectively eliminate postoperative bacterial intraocular invasion. Candidates for new methods include a newly synthesized drug-delivery hydrogel soft contact lens [88] and a modified intraocular lens (IOL) that functions as a drug-delivery device for sustained release of antibiotics [89]. Both approaches have been shown to deliver and sustain higher concentrations of fluoroquinolones in the anterior chamber compared to topical application. The modified IOL releases an initial burst of antibiotics that reach a concentration of approximately 10–20 times higher than topical instillation in the rabbit anterior chamber. There was no toxicity associated with the higher concentrations of antibiotics, and rabbit eyes with *S. epidermidis* endophthalmitis were efficiently treated after implantation of the hydrogel IOL drug-delivery system [89].

Whether or not achieving high antibiotic levels in the aqueous by any method at the end of surgery actually reduces the incidence of postoperative endophthalmitis is unclear, however. Prophylaxis for endophthalmitis is further discussed in Chap. 15. Intracameral injection of antibiotics can achieve high aqueous levels, and a multicenter randomized controlled trial performed in Europe (ESCRS or European Society of Cataract and Refractive Surgeons study) found that prophylactic

intracameral cefuroxime reduced the incidence of post-cataract endophthalmitis [85A]. However, the conclusion of the ESCRS study has been questioned because the endophthalmitis rate in the control group was high relative to rates seen in many U.S. centers, and endophthalmitis rates as low as those found in the cefuroxime group have been reported in the US and some European centers without use of intracameral antibiotic prophylaxis [90].

## 14.7 Conclusion

Resistance to commonly used antibiotics is a growing concern in ophthalmology. Antibiotic resistance rates in common endophthalmitis pathogens are steadily increasing, especially for the fluoroquinolone agents. Prophylactic topical application of fluoroquinolones, including the newest compounds moxifloxacin and gatifloxacin, is associated with the selection of highly resistant mutants in the microbiota of the ocular surface. Therefore, this current practice may result in the expansion of resistant populations, especially staphylococci, resulting in more refractory, persistent intraocular infections. In addition to the unproven efficacy of fluoroquinolones in preventing endophthalmitis following intraocular procedures, their use is associated with selecting resistant commensal organisms. With our growing understanding of the PK/PD of these antibiotics, it is unlikely that topical administration of fluoroquinolones would be effective in killing microbes in the anterior chamber. This highlights the need for prospective randomized studies to evaluate whether or not these topical antibiotics are really needed for preventing postoperative or post-injection endophthalmitis.

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# Chapter 15
# Preventing Endophthalmitis

**Marlene L. Durand**

## 15.1 Introduction

Endophthalmitis is a rare but potentially blinding infection. Vision loss after endophthalmitis is common and depends largely on the pathogen, with poor visual outcome (<20/100) occurring in 70–80 % of cases due to virulent pathogens such as streptococci and 10–20 % of cases that are culture-negative or due to coagulase-negative staphylococci [1]. The importance of preventing endophthalmitis is clear but the optimal method is unknown. Most endophthalmitis cases are exogenous, and commonly used prophylactic strategies vary according to the underlying risk factor – eye surgery, intravitreal injection, trauma, or presence of a filtering bleb or device such as a keratoprosthesis. The most accurate way of determining the efficacy of a particular prophylaxis for a given type of surgery or other risk factor is through a prospective randomized controlled trial, but few such trials have been performed. This is not surprising given the need for such a trial to enroll thousands of participants in order to detect a significant difference between the incidence of endophthalmitis in control and intervention groups. As a consequence, indirect evidence has been used as the basis of clinical practice for many types of prophylaxis. Table 15.1 summarizes the evidence for various types of prophylactic measures depending on the risk factor for endophthalmitis, and includes an estimate of how often these measures are used in clinical practice.

M.L. Durand, MD
Department of Medicine and Department of Ophthalmology, Harvard Medical School, Boston, MA, USA

Infectious Disease Service, Massachusetts Eye and Ear, Infectious Disease Unit, Massachusetts General Hospital, Boston, MA, USA
e-mail: mdurand@mgh.harvard.edu



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**Table 15.1** Endophthalmitis prophylaxis: scientific basis and common clinical practice

| Prophylaxis | Cataract surgery | Intravitreal injection | Penetrating trauma | Corneal transplant |
|---|---|---|---|---|
| Preoperative topical povidone-iodine | No RCT[a], but has become standard | No RCT, but commonly used | No RCT, but commonly used at the time of surgical repair | No RCT, but commonly used |
| Preoperative topical antibiotics | RCT of levofloxacin: no benefit | No RCT, not commonly used | No RCT | No RCT, not routinely used |
| Intracameral cefuroxime | RCT showed benefit (see text) | No RCT, not used | No RCT | No RCT, not routinely used |
| Other intracameral antibiotics | No RCT, rarely used | No RCT, not used | No RCT | No RCT, not used |
| Intravitreal antibiotics | No RCT, rarely used | No RCT, not used | 1 RCT showed benefit, another showed benefit in eyes with intraocular foreign body | No RCT, not used |
| Post-procedure topical antibiotics x several days | No RCT, but often used except in some countries (e.g., Sweden; see text) | No RCT; retrospective studies suggest use may even increase endophthalmitis rate | No RCT, often used | No RCT, often used |
| Masks or silence during procedure | Masks used (operating room attire) | No RCT, but retrospective studies suggest benefit | Masks used (operating room attire) | Masks used (operating room attire) |
| Systemic antibiotics | No RCT, not used | No RCT, not used | No RCT, but retrospective studies suggest benefit | No RCT, not used |

[a]*RCT* prospective randomized controlled trial

## 15.2 Eye Surgery

Eye surgery is a major risk factor for endophthalmitis. Most studies of postoperative endophthalmitis have focused on cataract surgery since this is one of the most common eye surgeries performed worldwide. See Chap. 5 for further discussion of acute-onset postoperative endophthalmitis. Cataract surgery is complicated by endophthalmitis in 0.01–0.2 % of cases. There has been one prospective randomized controlled trial of prophylaxis; other studies have been retrospective or have reported outcomes of indirect measures such as conjunctival colonization or aqueous contamination.

### *15.2.1 Povidone-Iodine (Topical)*

In 1991, Speaker and Menikoff reported the results of an open-label, nonrandomized trial that compared use of topical 5 % povidone-iodine (Betadine, Purdue Frederick Company, Norwalk, CT) versus the silver protein solution Argyrol (then made by Iolab Corporation, San German, PR) [2]. There was no control group. Patients were not randomized, but rather prophylaxis was given by floor – all cases performed in operating rooms on one floor (suite A) were compared with all cases performed on another floor (suite B). No attempt was made to control for differences in types of eye surgeries performed in the suites or differences in antibiotic prophylaxis used by various surgeons. Endophthalmitis rates were determined retrospectively, and surgeries were grouped into two categories, either "cataract and lens procedures, including secondary intraocular lens" (simplified here as cataract surgery), or "glaucoma, vitreoretinal, keratoplasty, and miscellaneous procedures." Suite A included significantly fewer non-cataract surgeries than suite B, 3 % versus 28 %. In Phase 1 of the study, all patients received Argyrol, and the culture-positive endophthalmitis rate for all types of surgeries was 0.18 % in suite A and 0.16 % suite B (0.11 and 0.14 %, respectively, for cataract surgery). In Phase 2, patients in suite A received povidone-iodine and the culture-positive endophthalmitis rate decreased to 0.06 %. Speaker and Menikoff concluded that povidone-iodine was more effective than Argyrol for prophylaxis in eye surgery, and since this publication, povidone-iodine has become the standard preoperative prophylaxis. However, if one compares the incidence of culture-positive endophthalmitis for the same category of surgery – cataract surgery – in the Speaker and Menikoff study, it is apparent that povidone-iodine and Argyrol were equally effective: the culture-positive endophthalmitis incidence was 0.06 % (2 of 3384 cases) in suite A versus 0.06 % (2 of 3289 cases) in suite B, $p = 1$. Is povidone-iodine more effective than no topical prophylaxis? No well-designed study has evaluated this. A randomized trial from Denmark of over 4100 cataract surgeries performed in 1981–1986 compared povidone-iodine eye drops in the conjunctival sac versus none and found no significant difference in endophthalmitis rates [3]. However, the study was limited by the lack of intraocular cultures; cases of endophthalmitis were diagnosed clinically.

Multiple microbiologic surveillance studies have demonstrated a decrease in the concentration of bacteria colonizing the conjunctiva following topical povidone-iodine use, or a decrease in intraocular contamination during surgery. Carrim and colleagues from Scotland cultured the conjunctivae of 54 patients prior to cataract surgery and found that 5 % povidone-iodine decreased the rate of positive conjunctival cultures from 87 to 30 % [4]. Shimada and colleagues from Japan used standard preoperative povidone-iodine prophylaxis but then during surgery, repeatedly irrigated the ocular surface with either balanced salt solution (2801 patients) or 0.25 % povidone-iodine (1606) and found that no patient in either group developed endophthalmitis [5]. They did find that vitreous cultures, obtained in 103 patients in each group, were more often positive in the

saline irrigation group (2 % versus 0 %). Li et al. from Germany performed conjunctival cultures after a 10 ml irrigation of the conjunctiva with either 1 %, 5 %, or 10 % povidone-iodine and concluded that 10 % had the greatest effect in reducing bacterial colonization [6]. No study to date has demonstrated that a reduction in the rate of positive cultures by microbiologic surveillance of conjunctiva or intraocular fluids correlates with a reduction in endophthalmitis incidence.

Retrospective studies have tried to determine whether preoperative povidone-iodine eye drops versus povidone-iodine irrigation of the conjunctiva is more effective as prophylaxis. Nentwich et al. reviewed the experience with 68,000 eye surgeries at a single German hospital from 1990 to 2009 during which the preoperative prophylactic regimen evolved from no standardized prophylaxis (1990–1992) to topical 10 % povidone-iodine on lid skin plus a drop of 1 % povidone-iodine in the conjunctiva (1993–1998), to topical povidone-iodine on lid skin and irrigation of the conjunctiva with 10 ml of 1 % povidone-iodine (1999–2009) [7]. The latest time period, with povidone-iodine irrigation, was associated with the lowest incidence of endophthalmitis, 0.04 % versus 0.34 % (first time period) and 0.22 % (second time period). However, other advances in surgical technique and perioperative care may be reflected in the reduction of endophthalmitis incidence in the latest time period, so the question of povidone-iodine eye drops versus irrigation remains unanswered.

### *15.2.2 Topical Antibiotics*

Applying a topical antibiotic to the conjunctiva reduces the colonizing flora, but no study has shown that this reduces the risk of endophthalmitis. Only one randomized prospective study, the European Society of Cataract and Refractive Surgeons (ESCRS) study, has been performed to evaluate the efficacy of preoperative topical antibiotic prophylaxis. That study randomized 16,200 cataract surgery patients in a $2 \times 2$ design to evaluate both the use of intracameral cefuroxime (discussed below) and the use of perioperative topical levofloxacin as prophylaxis. For the topical levofloxacin randomization, patients received either no topical antibiotic or topical levofloxacin given immediately perioperatively (two drops in the hour before and three drops in the 15 min immediately after surgery) [8]. Patients in both groups received topical levofloxacin for 6 days postoperatively. There was no difference in the endophthalmitis rate between these groups. The ESCRS study also demonstrated that clear cornea incisions versus scleral tunnel incisions increased endophthalmitis risk nearly sixfold, silicone versus acrylic intraocular lenses (IOLs) increased risk threefold, and surgical complications increased risk nearly fivefold, risk factors to consider when evaluating nonrandomized studies.

Many ophthalmologists give prophylactic topical antibiotics for several days postoperatively. However, no randomized controlled trial has ever been performed to evaluate the efficacy of this practice. Scandinavian countries do not

use postoperative antibiotic prophylaxis, and yet they have very low rates of post-cataract endophthalmitis. A center in Norway retrospectively evaluated 15,200 cataract surgeries in 2004–2011 and found that stopping postoperative topical chloramphenicol prophylaxis in 2007 did not lead to a significant difference in endophthalmitis rates (0.07 % with postoperative topical chloramphenicol, 0.05 % without) [9]. All cataract surgeries in this study (both before and after 2007) were performed with preoperative topical 5 % povidone-iodine drops, clear cornea incisions, acrylic IOLs, intracameral cefuroxime at the end of the case, and topical corticosteroids postoperatively. For many years, Sweden has used a prophylactic regimen that includes intracameral cefuroxime but not postoperative topical antibiotics, and Sweden's post-cataract endophthalmitis rates are some of the lowest worldwide. Sweden has maintained a very complete (95 % participation) registry of cataract surgeries since 1992, now with over a million cases in the data bank [10], so rates are presumably quite accurate. A recent review of 465,000 cataract surgeries performed in Sweden in 2005–2010 reported an endophthalmitis rate of only 0.03 % overall, and this rate was not lower in 14 % of patients who received postoperative topical antibiotics [11].

### *15.2.3 Intracameral Antibiotics*

Following the Swedish success in using intracameral cefuroxime as prophylaxis for cataract surgery, the ESCRS performed a multicenter randomized prospective study involving 24 hospitals in nine European countries during 2003–2006 [8]. Part of the 2×2 study design included randomization to intracameral injection of cefuroxime 1 mg/0.1 ml at the end of surgery. The study found that intracameral cefuroxime was associated with a significantly lower rate of postoperative endophthalmitis, 0.06 % versus 0.3 % in the control group. As a consequence of this study, intracameral cefuroxime prophylaxis is widely used in Europe, where 74 % of respondents in a recent survey said they use this or another intracameral antibiotic as prophylaxis [12]. Several retrospective studies from Europe have supported the ESCRS findings; in Ireland, for example, the endophthalmitis rate decreased from 0.5 to 0.06 % following adoption of intracameral cefuroxime prophylaxis [13]. However, the results of the ESCRS have been questioned because of the high rate of endophthalmitis in the control group. A number of centers have reported very low rates of endophthalmitis without use of prophylactic intracameral antibiotics. A center in Germany recently reported a 0.04 % postoperative endophthalmitis rate for surgeries performed in 1999–2009 using topical povidone-iodine but no intracameral cefuroxime [7].

Support for intracameral cefuroxime prophylaxis is high in many centers worldwide and likely to increase with the availability of a commercial preparation of intracameral cefuroxime. A 2014 survey of the American Society of Cataract and Refractive Surgery (ASCRS) members reported that 47 % currently used or planned

to use intracameral antibiotic prophylaxis for cataract surgery, although 50 % of nonusers said they would adopt the practice if a commercial product were available [14]. Whether an intracameral antibiotic other than cefuroxime would be effective as prophylaxis is unknown; none have been tested in a randomized controlled trial. Small observational studies have reported experience with using intracameral moxifloxacin, cefazolin, or vancomycin [15].

### *15.2.4 Other Types of Prophylaxis*

The efficacy of adding antibiotics to the irrigating fluids used during surgery, or of injecting subconjunctival antibiotics at the end of surgery, has never been evaluated by randomized prospective trials. Some studies have reported using aminoglycosides as prophylaxis, and this should be strongly discouraged given the potential retinal toxicity of these agents.

### *15.2.5 Summary: Preventing Postoperative Endophthalmitis*

For eye surgery, prophylactic preoperative topical povidone-iodine is widely used and well tolerated. This author recommends use of topical povidone-iodine recognizing that the scientific evidence supporting efficacy is only indirect (reduction in microbial colonization of the ocular surface and intraocular contamination during surgery). The addition of preoperative topical levofloxacin to standard povidone-iodine prophylaxis for cataract surgery was not beneficial in the ESCRS study. This author does not recommend preoperative topical antibiotics except in those rare patients who are allergic to topical povidone-iodine (a topical antibiotic can be given immediately preoperatively in such patients). The ESCRS study found that use of prophylactic intracameral cefuroxime was associated with a lower endophthalmitis rate (0.06 % versus 0.3 % in the control group), but the result has been questioned because of the high endophthalmitis rate in the control group. Prophylactic topical antibiotics are commonly prescribed postoperatively for several days but the efficacy of this prophylaxis is unknown. Recent retrospective studies from Norway and Sweden have reported very low rates of endophthalmitis with use of intracameral cefuroxime but without use of postoperative topical antibiotics. Studies from centers that do not use either prophylactic intracameral cefuroxime or postoperative topical antibiotics are lacking. This author believes that no recommendations can be made regarding use of postoperative prophylactic topical antibiotics except in centers that use intracameral cefuroxime: in those centers, postoperative antibiotic prophylaxis does not seem to be necessary.

## 15.3 Intravitreal Injections

Injections of antagonists to vascular endothelial growth factor (VEGF) are given repeatedly (as often as monthly) on a chronic basis to patients with neovascular age-related macular degeneration, and patients with macular edema from diabetes mellitus and retinal vein occlusion. As a consequence, the endophthalmitis risk is cumulative in these patients. There are also additional indications for anti-VEGF agents being studied, such as proliferative retinopathies (caused by diabetes, radiation, branch vein occlusions, sickle cell, etc.) and retinopathy of prematurity. In addition, the use of intravitreal corticosteroids for a variety of indications has increased in recent years. See Chap. 7 for further discussion of post-injection endophthalmitis. Because of the increasing use of intravitreal injections, the percentage of endophthalmitis cases due to post-injection endophthalmitis has continued to rise and is greater than the percentage due to post-cataract endophthalmitis at many centers worldwide.

There have been no randomized prospective studies evaluating the use of various prophylactic measures for intravitreal injections. These measures include use of lid speculums, povidone-iodine, post-injection topical antibiotics, masks, or observation of silence during injection. The use of lid speculums and prophylactic topical povidone-iodine is widely used.

### *15.3.1 Topical Antibiotics, Given Post-injection*

The use of prophylactic topical antibiotics following injection has not offered any apparent benefit. In two large studies, a retrospective case control study of 172,096 anti-VEGF injections [16] and a meta-analysis of the literature that included 445,503 anti-VEGF injections [17], the use of prophylactic post-injection antibiotics was actually associated with a higher risk of endophthalmitis.

### *15.3.2 Masks or Silence to Prevent Post-injection Streptococcal Endophthalmitis*

In large series, streptococci cause approximately 30 % of post-injection endophthalmitis cases versus approximately 10 % of postoperative cases. In a meta-analysis of 43 studies involving over 350,000 anti-VEGF injections worldwide and published 2005–2012, streptococci caused 29.4 % of culture-positive endophthalmitis cases [18]. A similar meta-analysis of the U.S. literature 2005–2009

found streptococci caused 30.8 % of culture-positive post-injection cases [19]. In contrast, three large series of cataract surgery found streptococci caused 9 % (Endophthalmitis Vitrectomy Study [20]), 8 % (clear cornea surgery [21]), and 12 % (Medicare claims for five U.S. states [22]), of culture-positive endophthalmitis cases following cataract surgery. Studies from single centers also show a difference between streptococcal endophthalmitis rates following intravitreal injections versus eye surgeries. A study from Houston found that viridans streptococci were cultured over three times more often in post-injection than in post-operative endophthalmitis cases [23]. A study from Australia found streptococci caused 24.5 % of post-injection but only 6.3 % of post-cataract endophthalmitis cases [24]. A study from Philadelphia found that streptococci caused 38 % of post-injection endophthalmitis cases versus 0 % of pars plana vitrectomy cases [25].

Streptococcal endophthalmitis is a dreaded complication of intravitreal injections because the resulting visual acuity is often poor; 70–80 % of patients are left with less than 20/100 vision in the affected eye. In one study, the visual acuity outcomes of the streptococcal endophthalmitis cases were count fingers in 33 %, hand motion in 33 %, and no light perception in 33 % [25]. Efforts to reduce post-injection streptococcal endophthalmitis have focused on reducing contamination of the eye by aerosolized oral flora. Viridans streptococci are common members of the oral flora, and oral flora bacteria may be aerosolized during speech. While masks are universally used by operating room personnel for cataract and other incisional eye surgeries, they are infrequently used for intravitreal injections performed in the office setting. It has been known for years from the anesthesiology literature that masks prevent the dispersal of oral flora bacteria that occurs during speech [26] and several recent studies in the ophthalmology literature have demonstrated the same thing. A study of volunteers given a 5-min script to read either reclined in an ophthalmology examination chair with an agar plate taped to their forehead to mimic a talking patient, or standing in an ophthalmologist's position over the subject, found that significantly less bacterial contamination of the agar plates occurred when masks were worn or silence was observed [27]. Oral flora streptococcal species comprised over two-thirds of the bacterial colonies that grew on culture plates in the no mask group. In another study, volunteers spoke for 30 seconds above agar plates placed 30 cm below their mouths; fewer bacteria grew on the agar plates if masks were used or silence was observed [28].

Clinical studies have supported the efficacy of masks or silence in preventing post-injection endophthalmitis, especially due to streptococci. A study from Denmark demonstrated an endophthalmitis rate of zero in 20,293 intravitreal injections performed in the operating room with the usual masks and gowns [29]. In an analysis of the worldwide literature 2006–2013 regarding bevacizumab and ranibizumab injections, Sigford and colleagues found no cases of

streptococcal endophthalmitis in series from Europe, where injections are primarily given in the operating room [17]. A study of 25 centers in France involving 316,576 intravitreal injections (anti-VEGF or corticosteroids), most procedures performed in operating rooms but all performed with patient and surgeon wearing masks, the culture-positive endophthalmitis rate was low (0.007 %) and only one (4 %) of the culture-positive cases were due to streptococci [30]. The office setting will continue to be the usual location for intravitreal injections in many centers in the U.S. and elsewhere, so use of masks or a strict no-talking policy during injection has been evaluated. Sigford and colleagues found no streptococcal endophthalmitis cases in centers that specified mask use for injections [17]. A study from Philadelphia found that instituting a strict "no-talking" policy for office-based injections led to a significant reduction of post-injection endophthalmitis from 0.02 to 0.01 % and a significant reduction in endophthalmitis cases due to oral flora pathogens from 0.015 to 0.002 % [31].

### *15.3.3 Summary: Preventing Post-injection Endophthalmitis*

For preventing post-injection endophthalmitis, the use of a lid speculum and topical povidone-iodine is widely used. Endophthalmitis due to viridans streptococci appears to occur more frequently after intravitreal injections than after post-cataract surgery when injections are performed in the office setting without use of masks. Aerosols of oral flora that occur during speech are a potential source of ocular surface contamination and may be the source of some post-vitrectomy endophthalmitis cases. The use of masks or adhering to a strict no-talking policy has been effective in reducing the overall incidence of post-injection endophthalmitis and particularly the incidence of streptococcal endophthalmitis. For this reason, this author recommends use of masks or observing a strict no-talking policy. The use of prophylactic topical antibiotics post-injection has not proven beneficial and is not recommended.

## 15.4 Penetrating Eye Trauma

Endophthalmitis develops in 1–7 % of eyes that suffer penetrating ocular trauma (open-globe injury) [32–35]. See Chap. 9 for further discussion of post-traumatic endophthalmitis. Risk factors for post-traumatic endophthalmitis include delay in presentation or repair, rural setting or wounds contaminated by vegetable matter, lens capsule disruption, and retained foreign body.

### 15.4.1 Repair of Open Globe Injuries

Prompt surgical repair, within 24 h of presentation, is recommended by multiple studies and decreases the risk of post-traumatic endophthalmitis.

### 15.4.2 Intravitreal Antibiotics

There have been few randomized prospective trials to evaluate the efficacy of antibiotics in preventing endophthalmitis following penetrating trauma, and these have focused on prophylactic intravitreal antibiotics. Narang and colleagues in India randomized 70 consecutive patients with open-globe injuries to receive prophylactic intravitreal antibiotics (vancomycin plus ceftazidime) or no intravitreal antibiotics at the time of primary repair; the antibiotic group had a lower incidence of endophthalmitis (6 % versus 18 %) [36]. Soheilian and colleagues in a multicenter, randomized, double-blind trial in Iran involving 346 eyes with penetrating eye injury found that use of prophylactic intravitreal antibiotics (clindamycin and gentamicin) was associated with a lower incidence of endophthalmitis, but this was significant only in eyes with an intraocular foreign body [37]. All patients in that study also received 5 days of postoperative intravenous antibiotics. In centers that choose to use intravitreal antibiotics for post-traumatic endophthalmitis prophylaxis, intravitreal vancomycin plus ceftazidime would be better choices than clindamycin and gentamicin given the potential retinal toxicity of aminoglycosides and the increasing rate of clindamycin resistance in staphylococci.

### 15.4.3 Systemic Antibiotics

Systemic antibiotics are often started prophylactically when patients present with open globe injuries and continued for two or more days. Although no prospective trial has evaluated the efficacy of systemic antibiotics for prophylaxis, a retrospective review of 558 cases with open-globe injuries treated at the Massachusetts Eye and Ear reported a very low rate (0.9 %) of post-traumatic endophthalmitis using a standardized approach that included 48 h of prophylactic intravenous vancomycin plus ceftazidime (or vancomycin plus a fluoroquinolone in penicillin-allergic patients) [32]. Some authors recommend use of prophylactic intravitreal antibiotics in high-risk eyes, including those with a history of soil contamination, with or without systemic antibiotic prophylaxis [38]. Other experts recommend intravitreal plus systemic antibiotic prophylaxis particularly for eyes with intraocular foreign bodies (see Chap. 9).

### *15.4.4 Topical Antibiotics*

The value of topical antibiotic prophylaxis has not been assessed. Topical antibiotics are often given post-repair of the open globe injury.

### *15.4.5 Summary: Preventing Post-traumatic Endophthalmitis*

Prompt repair of open globe injuries and at least 48 h of systemic antibiotics has been associated with a low rate of post-traumatic endophthalmitis. The Massachusetts Eye and Ear protocol uses intravenous vancomycin plus ceftazidime for 48 h and has been associated with a very low post-traumatic endophthalmitis rate (0.9 %) as noted above, but other prophylactic regimens have also been beneficial (see Chap. 9). Prophylactic intravitreal antibiotics injected at the time of surgical repair may confer benefit to high-risk eyes, particularly those with intraocular foreign bodies.

## 15.5 Corneal Transplantation (Penetrating Keratoplasty)

Penetrating keratoplasty (PK) is complicated by acute postoperative endophthalmitis in approximately 0.17 % of cases [39, 40]. There are two main questions regarding whether or not this relatively high endophthalmitis rate can be further reduced. First, does a positive donor rim culture indicate the need for postoperative antibiotic prophylaxis? Secondly, should the storage media used in the U.S. for donor corneas contain an antifungal agent in addition to the antibacterial agents currently included?

### *15.5.1 Donor Rim Cultures*

The rim of donor cornea left after the central donor corneal button is removed for PK is often cultured, although the utility of these cultures has been debated. An argument can be made for routine culture even though positive donor rim cultures are common. A comprehensive review of the literature has been performed by Wilhelmus and colleagues, who found that 14 % of the 17,614 corneal grafts included in their review had positive donor rim cultures but only 0.2 % developed endophthalmitis [41]. Of these endophthalmitis cases, evaluation of bacterial endophthalmitis cases showed 55 % concordance with donor rim cultures (same organism in 11 of 20 cases) and 100 % concordance with rim cultures in *Candida* endophthalmitis cases (10 of 10 cases). Considering three relevant studies for

bacterial isolates and six for fungal isolates, Wilhelmus et al. found that the odds ratio for developing bacterial endophthalmitis if the donor rim grew bacteria versus no bacteria was 17.5 (95 % confidence interval 2.9–104.6), while the odds ratio for developing fungal endophthalmitis if the donor rim grew fungi versus no fungi was 247 (95 % confidence interval 68–894). Using Bayesian analysis, Wilhemus and colleagues found that a positive donor rim culture overall increased the risk of developing endophthalmitis fivefold, from 0.2 to 1 %, while a donor rim culture positive for *Candida* predicted a 3 % probability of the transplanted eye developing post-PK *Candida* endophthalmitis. A high (91 %) concordance between post-PK *Candida* endophthalmitis and donor rim or corneal storage media cultures was reported by Merchant et al. as well [42]. Nearly all post-PK *Candida* endophthalmitis cases are due to *C. albicans* and *C. glabrata.*

### *15.5.2 Storage Media for Donor Corneas*

In Europe, most eye banks use a storage medium for donor corneas that is kept at 30–37 °C and includes amphotericin in addition to antibacterial agents. In North America, donor corneas are stored at 2–8 °C and the medium used (Optisol-GS, Bauch & Lomb, Inc) contains gentamicin and streptomycin but no antifungal agent. Experimental studies have shown a reduction in fungal growth when a *Candida*-contaminated storage medium contains amphotericin [43] and reduction of corneal rim cultures positive for fungi when voriconazole is added to Optisol [44]. The Eye Bank Association of America (EBAA) reviewed their voluntary online adverse reaction reporting system from 2007 to 2010 and identified 14 fungal keratitis cases and 17 fungal endophthalmitis cases out of 221,664 corneal transplants performed [45]. In 15 eyes that received the mate corneas, 10 (67 %) also developed fungal endophthalmitis or keratitis. Two trends were noted although neither reached statistical significance: fungal infections increased over time, and endothelial keratoplasty procedures carried a higher risk of fungal infections than did PK (0.02 % versus 0.01 %). The EBAA concluded that there was not sufficient evidence to pursue adding antifungal agents to the donor storage media.

### *15.5.3 Summary: Preventing Post-keratoplasty Endophthalmitis*

The risk of developing post-keratoplasty endophthalmitis increases from 0.2 to 1 % overall in patients who receive a cornea whose rim culture grows a microbe and to 3 % if that microbe is *Candida*. Concordance with donor rim cultures and subsequent endophthalmitis is 55 % for bacteria but 90–100 % for *Candida. Candida*

usually grows rapidly on routine culture media (e.g., 1–4 days). This author believes that if the donor rim culture grows bacteria, the significance of this is uncertain so no recommendations regarding prophylaxis can be made. However, if the donor rim grows *Candida*, the patient has a 3 % chance of developing *Candida* endophthalmitis, and this author recommends that ophthalmologists follow such patients very closely in the postoperative period for early signs of fungal endophthalmitis. It is unknown whether such patients should be treated with a brief pulse (e.g., 1–3 days) of a prophylactic antifungal agent (e.g., topical voriconazole or oral fluconazole), but this author believes such prophylaxis should be considered especially when rim culture growth of *Candida* is moderate to abundant. The use of antifungal agents in storage media may decrease the rate of posttransplant *Candida* endophthalmitis.

## 15.6 Delayed-Onset Endophthalmitis in Eyes with a Filtering Bleb, Glaucoma Drainage Device, or Keratoprosthesis

Endophthalmitis is always a risk in patients who have an indwelling filtering bleb, glaucoma drainage device (GDD), or an artificial cornea (keratoprosthesis) and in most cases occur abruptly but months to years postoperatively. Cases are usually due to virulent pathogens such as streptococci, and visual outcome is often poor. No randomized controlled studies have been performed to assess the optimal method of prophylaxis.

### *15.6.1 Bleb-Related Endophthalmitis*

Large studies of patients with glaucoma filtering blebs have reported an endophthalmitis incidence of 1.3–1.4 % within 5 years of surgery [46, 47]. The average onset of infection was 33 months in one study [47]. Some cases of endophthalmitis are preceded by blebitis. A history of bleb leakage increases the risk of developing a bleb-related infection (i.e., blebitis, endophthalmitis) by as much as 4.7 times [46]. Prompt surgical repair of leaking blebs has been recommended by several authors to reduce the incidence of bleb-related infections [48]. While routine use of chronic topical prophylactic antibiotics in eyes with filtering blebs is not recommended, prompt treatment with topical antibiotics is recommended at the earliest signs of blebitis. Many cases of bleb-related endophthalmitis have a rapid onset and poor visual outcome. Aside from repair of bleb leaks, rapid treatment of bleb-related infections is important in order to reduce the incidence of endophthalmitis. As detailed by Dr. Yamamoto in Chap. 8, patients with filtering blebs should be educated regarding warning signs of infection, seek medical attention promptly if they see any such sign, and start empiric topical antibiotics if they cannot immediately see an ophthalmologist.

### 15.6.2 Glaucoma Drainage Device

Endophthalmitis in eyes with a GDD usually occurs months to years postoperatively and presents as an acute infection, as discussed in Chap. 12. Conjunctival erosion over the device – usually over the tube – is often evident and is a significant risk factor for endophthalmitis. The incidence of endophthalmitis is 1–2 % in studies with 1–5 years of follow-up, with a higher incidence (4.4–5.8 %) reported in children [49, 50]. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common pathogens in GDD-related endophthalmitis, although other pathogens have been described as etiologies. Prompt surgical repair of any conjunctival erosion over the device is important and has been recommended [51]. Local infections associated with these erosions should be treated with antibiotics. As discussed below, pneumococcal vaccination may be valuable in preventing some cases of endophthalmitis in patients with GDDs.

### 15.6.3 Keratoprosthesis

Endophthalmitis in eyes with a keratoprosthesis (KPro) resembles bleb-related and GDD-related endophthalmitis in that infection often occurs suddenly months to years postoperatively. It is often due to virulent bacteria and visual outcome is poor as a consequence. Endophthalmitis related to KPros is described in Chap. 12. Many KPro eyes also have a GDD or filtering bleb, potentially increasing the endophthalmitis risk. The most widely used KPro is the Boston KPro, and broad-spectrum topical antibiotics are given daily for prophylaxis for the duration of the device. No randomized trial has evaluated use versus no use of topical prophylactic antibiotics in KPro eyes, but such a trial is very unlikely to be proposed. There have been several well-documented cases of acute endophthalmitis developing shortly after the patient stopped using prophylactic topical antibiotic eye drops, with devastating visual outcome. As discussed below, in addition to daily topical antibiotics for the duration of the device, this author recommends patients receiving a KPro be vaccinated against *S. pneumoniae* (commonly known by patients as the “pneumonia shot”).

### 15.6.4 Vaccination

Although there is no vaccination available against viridans streptococci, there are two pneumococcal vaccinations available, and these are already recommended for many patients by the Centers for Disease Control and Prevention

(CDC) to protect against *S. pneumoniae*. Children age 5 and under routinely receive the 13-valent conjugated pneumococcal vaccine (PCV13) in several doses beginning at age 2 months, and adults age 65 and older are supposed to receive both the 13-valent and 23-valent vaccines (PPSV23), spaced at times specified by the CDC. However, adult compliance with this recommendation is suboptimal. Some patients age 6–64 not previously vaccinated with the 13-valent vaccine are also candidates for this vaccine if they have certain risk factors specified by the CDC. Some patients age 2–64 are also recommended to receive the 23-valent vaccine if they are immunocompromised, have a cochlear implant, or have certain chronic conditions such as diabetes, heart disease, lung disease, etc. Smoking and asthma have recently been added to the list of indications for the 23-valent vaccine in patients age 19–64. To date, eye conditions have not been included in this list of indications for either PCV13 or PPSV23, but this author believes filtering blebs, GDDs, and keratoprostheses should be included in the CDC list of indications for pneumococcal vaccination. Pneumococcal vaccination has been previously recommended by this author [52] and others [53] for patients with filtering blebs and by this author and colleagues for the Boston Keratoprosthesis [54]. Because many patients with filtering blebs, GDDs, or a keratoprosthesis are already candidates for pneumococcal vaccination based on current CDC guidelines, ophthalmologists should educate patients about the importance of getting pneumococcal vaccination from their primary care provider as this may prevent a potentially blinding eye infection.

### *15.6.5 Summary: Preventing Endophthalmitis after Blebs, Glaucoma Drainage Devices, Keratoprostheses*

Endophthalmitis in eyes with a filtering bleb, GDD, or KPro typically develops suddenly but months to years postoperatively. The incidence of endophthalmitis in eyes with a filtering bleb is 1.3 % or higher during the first 5 years postoperatively, and some cases are preceded by blebitis. This author recommends (as do others; see Chap. 8) that patients with filtering blebs should be educated regarding warning signs of infection, seek medical attention promptly if they see any such sign, and start empiric topical antibiotics if they cannot immediately see an ophthalmologist. In eyes with GDDs, conjunctival erosion is a major risk factor for endophthalmitis. This author recommends that any conjunctival erosion over a GDD should be immediately repaired; local infections should be promptly treated with antibiotics. For patients with a KPro, this author recommends daily topical antibiotic prophylaxis for the duration of the device (see Chap. 12 for discussion of antibiotic choice). For any patient with a filtering bleb, GDD, or KPro, this author recommends pneumococcal vaccination as described above.

## 15.7 Conclusion

The optimal endophthalmitis prophylaxis for most types of eye procedures is unknown because few randomized controlled trials have been performed. Such trials are difficult because thousands of patients have to be enrolled in order to detect a significant difference in treatment and control groups. The few randomized controlled trials that have been performed are reviewed here, along with the many retrospective studies and microbiologic surveillance studies that have been published. Endophthalmitis remains a rare infection, but hopefully future studies will help identify additional effective prophylactic measures.

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