Chapter 17
Endophthalmitis Caused by Gram-Negative Bacteria

Nidhi Relhan and Harry W. Flynn Jr.

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

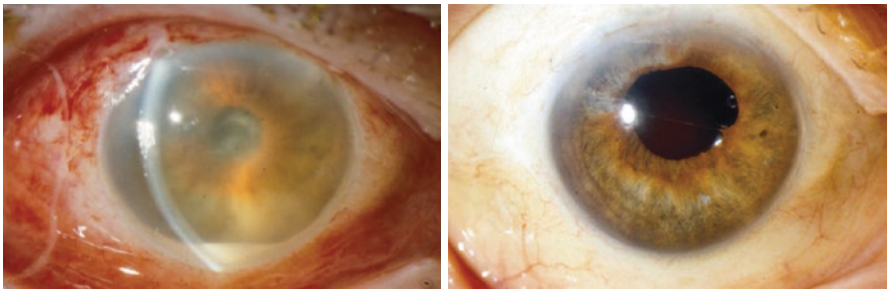

Fig. 17.1 (*Left*) Patient with postoperative endophthalmitis on day 1 after cataract surgery. Managed with pars plana vitrectomy and intravitreal antibiotics. (*Right*) Quiet eye showing resolved infection at 6-month follow-up. Vitreous grew *Serratia marcescens* and was sensitive to aminoglycosides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

N. Relhan, M.D. • H.W. Flynn Jr., M.D. (✉)
Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 900 N.W., 17th Street, Miami, Florida 33136, USA
e-mail: dr.nidhirelhan@gmail.com; hflynn@med.miami.edu

T. Das (ed.), *Endophthalmitis*, https://doi.org/10.1007/978-981-10-5260-6_17

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

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

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

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

Prevalence and Classification

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

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

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

Virulence Factors and Pathogenesis

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

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

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

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

Specific Gram-Negative Endophthalmitis

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

Endophthalmitis Caused by Proteus Species

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

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

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

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

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

Endophthalmitis Caused by Klebsiella Species

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

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

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

Endophthalmitis Caused by Achromobacter Species

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

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

Endophthalmitis Caused by Serratia Species

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

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

Endophthalmitis Caused by Pseudomonas Species

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

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

Endophthalmitis Caused by Haemophilus Species

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

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

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

Antimicrobial Susceptibilities

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

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

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

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

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

Diagnosis

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

Treatment Options

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

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

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

(continued)

Table 17.4 (continued)

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

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

Drugs by intravenous route are used for endogenous endophthalmitis cases

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

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

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

Summary

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

Acknowledgment We acknowledge support from NIH Center Core Grant P30EY014801 (Bethesda, Maryland), Research to Prevent Blindness Unrestricted Grant (New York, New York), and the Department of Defense (DOD Grant #W81XWH-09-1-0675) (Washington, DC).

Frequently Asked Questions

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

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

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

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

References

1. Han DP, Wisniewski SR, Wilson LA, et al. Spectrum and susceptibilities of microbiologic isolates in the Endophthalmitis Vitrectomy Study. Am J Ophthalmol. 1996;122(1):1–17.
2. Kamalarajah S, Silvestri G, Sharma N, et al. Surveillance of endophthalmitis following cataract surgery in the UK. Eye (Lond). 2004;18(6):580–7.
3. Altan T, Acar N, Kapran Z, et al. Acute-onset endophthalmitis after cataract surgery: success of initial therapy, visual outcomes, and related factors. Retina. 2009;29(5):606–12.
4. Jindal A, Pathengay A, Khera M, et al. Combined ceftazidime and amikacin resistance among Gram-negative isolates in acute-onset postoperative endophthalmitis: prevalence, antimicrobial susceptibilities, and visual acuity outcome. J Ophthalmic Inflamm Infect. 2013;3(1):62.
5. Wilhelmus KR. The pathogenesis of endophthalmitis. Int Ophthalmol Clin. 1987;27(2):74–81.
6. Ramachandran G. Gram-positive and gram-negative bacterial toxins in sepsis: a brief review. Virulence. 2014;5(1):213–8.
7. Puliafito CA, Baker AS, Haaf J, Foster CS. Infectious endophthalmitis. Review of 36 cases. Ophthalmology. 1982;89(8):921–9.
8. Kattan HM, Flynn HW Jr, Pflugfelder SC, et al. Nosocomial endophthalmitis survey. Current incidence of infection after intraocular surgery. Ophthalmology. 1991;98(2):227–38.
9. Leng T, Flynn HW Jr, Miller D, et al. Endophthalmitis caused by proteus species: antibiotic sensitivities and visual acuity outcomes. Retina. 2009;29(7):1019–24.
10. Sheu SJ, Kung YH, Wu TT, et al. Risk factors for endogenous endophthalmitis secondary to *klebsiella pneumoniae* liver abscess: 20-year experience in Southern Taiwan. Retina. 2011;31(10):2026–31.
11. Sng CC, Jap A, Chan YH, Chee SP. Risk factors for endogenous *Klebsiella* endophthalmitis in patients with *Klebsiella* bacteraemia: a case-control study. Br J Ophthalmol. 2008;92(5):673–7.
12. Lin JC, Chang FY, Fung CP, et al. Do neutrophils play a role in establishing liver abscesses and distant metastases caused by *Klebsiella pneumoniae*? PLoS One. 2010;5(11):e15005.
13. Scott IU, Matharoo N, Flynn HW Jr, Miller D. Endophthalmitis caused by *Klebsiella* species. Am J Ophthalmol. 2004;138(4):662–3.
14. Kashani AH, Eliott D. The emergence of *Klebsiella pneumoniae* endogenous endophthalmitis in the USA: basic and clinical advances. J Ophthalmic Inflamm Infect. 2013;3(1):28.
15. Kashani AH, Eliott D. Bilateral *Klebsiella pneumoniae* (K1 serotype) endogenous endophthalmitis as the presenting sign of disseminated infection. Ophthalmic Surg Lasers Imaging. 2011;42:e12–4.
16. Chen X, Adelman RA. Microbial spectrum and resistance patterns in endophthalmitis: a 21-year (1988-2008) review in northeast United States. J Ocul Pharmacol Ther. 2012;28(4):329–34.
17. Okada AA, Johnson RP, Liles WC, et al. Endogenous bacterial endophthalmitis. Report of a ten-year retrospective study. Ophthalmology. 1994;101(5):832–8.
18. Schiedler V, Scott IU, Flynn HW Jr, et al. Culture-proven endogenous endophthalmitis: clinical features and visual acuity outcomes. Am J Ophthalmol. 2004;137(4):725–31.
19. Sridhar J, Flynn HW Jr, Kuriyan AE, et al. Endophthalmitis caused by *Klebsiella* species. Retina. 2014;34(9):1875–81.
20. Sanghi S, Pathengay A, Jindal A, et al. Acute-onset postoperative endophthalmitis caused by multidrug-resistant *Klebsiella pneumoniae*. Clin Ophthalmol. 2014;8:1783–5.

21. Mandell WF, Garvey GJ, Neu HC. *Achromobacter xylosoxidans* bacteremia. Rev Infect Dis. 1987;9(5):1001–5.
22. Spear JB, Fuhrer J, Kirby BD. *Achromobacter xylosoxidans* (Alcaligenes xylosoxidans subsp. xylosoxidans) bacteremia associated with a well-water source: case report and review of the literature. J Clin Microbiol. 1988;26(3):598–9.
23. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev. 2002;15(2):167–93.
24. Reddy AK, Garg P, Shah V, Gopinathan U. Clinical, microbiological profile and treatment outcome of ocular infections caused by *Achromobacter xylosoxidans*. Cornea. 2009;28(10):1100–3.
25. Villegas VM, Emanuelli A, Flynn HW Jr, et al. Endophthalmitis caused by *Achromobacter xylosoxidans* after cataract surgery. Retina. 2014;34(3):583–6.
26. Sridhar J, Kuriyan AE, Flynn HW Jr, et al. Endophthalmitis caused by *Serratia marcescens*: clinical features, antibiotic susceptibilities, and treatment outcomes. Retina. 2015;35(6):1095–100.
27. Aaberg TM Jr, Flynn HW Jr, Schiffman J, Newton J. Nosocomial acute-onset postoperative endophthalmitis survey. A 10-year review of incidence and outcomes. Ophthalmology. 1998;105(6):1004–10.
28. Cheng JH, Chang YH, Chen CL, et al. Acute endophthalmitis after cataract surgery at a referral centre in Northern Taiwan: review of the causative organisms, antibiotic susceptibility, and clinical features. Eye (Lond). 2010;24(8):1359–65.
29. Zaluski S, Clayman HM, Karsenti G, et al. *Pseudomonas aeruginosa* endophthalmitis caused by contamination of the internal fluid pathways of a phacoemulsifier. J Cataract Refract Surg. 1999;25(4):540–5.
30. Ramappa M, Majji AB, Murthy SI, et al. An outbreak of acute post-cataract surgery *Pseudomonas* sp. endophthalmitis caused by contaminated hydrophilic intraocular lens solution. Ophthalmology. 2012;119(3):564–70.
31. Swaddiwudhipong W, Tangkitchot T, Silarug N. An outbreak of *Pseudomonas aeruginosa* postoperative endophthalmitis caused by contaminated intraocular irrigating solution. Trans R Soc Trop Med Hyg. 1995;89(3):288.
32. Mateos I, Valencia R, Torres MJ, et al. Nosocomial outbreak of *Pseudomonas aeruginosa* endophthalmitis. Infect Control Hosp Epidemiol. 2006;27(11):1249–51.
33. Maltezou HC, Pappa O, Nikolopoulos G, et al. Postcataract surgery endophthalmitis outbreak caused by multidrug-resistant *Pseudomonas aeruginosa*. Am J Infect Control. 2012;40(1):75–7.
34. Tenover FC. Mechanisms of antimicrobial resistance in bacteria. Am J Med. 2006;119(6 Suppl 1):S3–10. discussion S62–70.
35. Sridhar J, Kuriyan AE, Flynn HW Jr, Miller D. Endophthalmitis caused by *Pseudomonas aeruginosa*: clinical features, antibiotic susceptibilities, and treatment outcomes. Retina. 2015;35(6):1101–6.
36. Irvine WD, Flynn HW Jr, Miller D, Pflugfelder SC. Endophthalmitis caused by gram-negative organisms. Arch Ophthalmol. 1992;110(10):1450–4.
37. Recchia FM, Baumal CR, Sivalingam A, et al. Endophthalmitis after pediatric strabismus surgery. Arch Ophthalmol. 2000;118(7):939–44.
38. Scott IU, Flynn HW Jr, Feuer W, et al. Endophthalmitis associated with microbial keratitis. Ophthalmology. 1996;103(11):1864–70.
39. Yoder DM, Scott IU, Flynn HW Jr, Miller D. Endophthalmitis caused by *Haemophilus influenzae*. Ophthalmology. 2004;111(11):2023–6.
40. Kunimoto DY, Das T, Sharma S, et al. Microbiologic spectrum and susceptibility of isolates: part I. Postoperative endophthalmitis. Endophthalmitis Research Group. Am J Ophthalmol. 1999;128(2):240–2.
41. Asbell PA, Sanfilippo CM, Pillar CM, et al. Antibiotic resistance among ocular pathogens in the United States: five-year results from the antibiotic resistance monitoring in ocular microorganisms (ARMOR) surveillance study. JAMA Ophthalmol. 2015;133(12):1445–54.

42. Pathengay A, Moreker MR, Puthussery R, et al. Clinical and microbiologic review of culture-proven endophthalmitis caused by multidrug-resistant bacteria in patients seen at a tertiary eye care center in southern India. Retina. 2011;31(9):1806–11.
43. Gad GF, Mohamed HA, Ashour HM. Aminoglycoside resistance rates, phenotypes, and mechanisms of Gram-negative bacteria from infected patients in upper Egypt. PLoS One. 2011;6(2):e17224.
44. Strateva T, Yordanov D. Pseudomonas aeruginosa - a phenomenon of bacterial resistance. J Med Microbiol. 2009;58(Pt 9):1133–48.
45. Miller D. Microbiologic diagnosis in endophthalmitis. In: Durand LM, Miller WJ, Young HL, editors. Endophthalmitis. Cham: Springer International Publishing; 2016.
46. Radhika M, Mithal K, Bawdekar A, et al. Pharmacokinetics of intravitreal antibiotics in endophthalmitis. J Ophthalmic Inflamm Infect. 2014;4:22.
47. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS. The Sanford guide to antimicrobial therapy. 46th ed. Sperryville, VA: Antimicrobial Therapy Inc.; 2016.
48. Rooney P, Bilbe G, Zak O, O'Reilly T. Dexamethasone treatment of lipopolysaccharide-induced meningitis in rabbits that mimics magnification of inflammation following antibiotic therapy. J Med Microbiol. 1995;43(1):37–44.
49. Townsend GC, Scheld WM. The use of corticosteroids in the management of bacterial meningitis in adults. J Antimicrob Chemother. 1996;37(6):1051–61.
50. Maxwell DP Jr, Brent BD, Diamond JG, Wu L. Effect of intravitreal dexamethasone on ocular histopathology in a rabbit model of endophthalmitis. Ophthalmology. 1991;98(9):1370–5.
51. Park SS, Samiy N, Ruoff K, et al. Effect of intravitreal dexamethasone in treatment of pneumococcal endophthalmitis in rabbits. Arch Ophthalmol. 1995;113(10):1324–9.
52. Smith MA, Sorenson JA, D'Aversa G, et al. Treatment of experimental methicillin-resistant Staphylococcus epidermidis endophthalmitis with intravitreal vancomycin and intravitreal dexamethasone. J Infect Dis. 1997;175(2):462–6.
53. Yoshizumi MO, Lee GC, Equi RA, et al. Timing of dexamethasone treatment in experimental Staphylococcus aureus endophthalmitis. Retina. 1998;18(2):130–5.
54. Das T, Jalali S, Gothwal VK, et al. Intravitreal dexamethasone in exogenous bacterial endophthalmitis: results of a prospective randomised study. Br J Ophthalmol. 1999;83(9):1050–5.
55. Shah GK, Stein JD, Sharma S, et al. Visual outcomes following the use of intravitreal steroids in the treatment of postoperative endophthalmitis. Ophthalmology. 2000;107(3):486–9.
56. Meredith TA, Aguilar HE, Drews C, et al. Intraocular dexamethasone produces a harmful effect on treatment of experimental Staphylococcus aureus endophthalmitis. Trans Am Ophthalmol Soc. 1996;94:241–52. discussion 52–7.
57. Callegan MC, Engelbert M, Parke DW II, et al. Bacterial endophthalmitis: epidemiology, therapeutics, and bacterium-host interactions. Clin Microbiol Rev. 2002;15(1):111–24.