Prevention, diagnosis, and management of acute postoperative bacterial endophthalmitis

Mark Packer, MD, David F. Chang, MD, Steven H. Dewey, MD, Brian C. Little, MD, Nick Mamalis, MD, Thomas A. Oetting, MD, Audrey Talley-Rostov, MD, Sonia H. Yoo, MD, for the ASCRS Cataract Clinical Committee

This distillation of the peer-reviewed scientific literature on infection after cataract surgery summarizes background material on epidemiology, etiology, and pathogenesis, describes the roles of surgical technique and antibiotic prophylaxis in prevention, and discusses diagnostic and therapeutic interventions in cases of suspected endophthalmitis.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2011; 37:1699–1714 © 2011 ASCRS and ESCRS

In the absence of conclusive evidence, ophthalmic surgeons face considerable uncertainty about the best way to prevent postsurgical infections. In this review, we have attempted to summarize current knowledge of infection prophylaxis, diagnosis, and treatment to provide a foundation for future research and enable surgeons to assess current options and practices.

CLINICAL AND SCIENTIFIC BACKGROUND

Epidemiology

Incidence/Prevalence Postoperative bacterial endophthalmitis has been reported to occur in from 0.04% to 0.2% of cataract surgical cases.[1] There appeared to be an increase in the incidence of endophthalmitis reported in the United States approximately a decade ago.[2] Using Medicare data, West et al.[3] found that the rate of endophthalmitis increased in 1998. Taban et al.[2] found an increased rate of endophthalmitis associated with phacoemulsification through clear corneal versus scleral tunnel incisions between 1992 and 2003. A large 10-year study performed at the Moran Eye Center of the University of Utah[4] found that the rate of postoperative endophthalmitis from 1997 through 2003 was 0.197%. From late 2003 to 2007, a period coincident with the adoption of fourth-generation

fluoroquinolones, the incidence of postoperative endophthalmitis dropped to 0.056%.[4]

Outside the U.S., the Swedish national reporting database identified an endophthalmitis incidence of 0.05% in a cohort of over 225 000 cases.[5] At one of the regional Aravind Eye Hospitals in India,[6] an analysis of over 42 000 consecutive cases, including manual extracapsular and phacoemulsification techniques using standardized sterilization and prophylaxis protocols, found the incidence of postoperative endophthalmitis over a period of almost 2 years was 0.09%. Two studies performed in Canada found similar rates of endophthalmitis after cataract surgery —0.14% to 0.15%.[7,8]

Reporting of cases is complicated by the fact that many cases of presumed endophthalmitis are culture negative. Culture results of cases in the Endophthalmitis Vitrectomy Study (EVS)[9] showed 69% with confirmed bacterial growth, 18% with no growth of an organism, and 13% with equivocal growth. In addition, cases of acute sterile postoperative inflammation, such as those that occur in the toxic anterior segment syndrome (TASS), can be mistaken for postoperative endophthalmitis.[10]

Antibiotics are used preoperatively and postoperatively to prevent endophthalmitis; however, no randomized controlled clinical trial has demonstrated the prophylactic benefit of any preoperative or postoperative topical antibiotic. The European Society of Cataract and Refractive Surgeons (ESCRS) Endophthalmitis Study[11] showed that intracameral cefuroxime was effective in reducing the rate of endophthalmitis almost 5-fold. Unfortunately, the

study's control group did not reflect the current prophylactic antibiotic practices using topical fourth-generation fluoroquinolones immediately before and after cataract surgery.

The cost of performing a large randomized study of antibiotic use for the prevention or treatment of endophthalmitis in the U.S. is prohibitive; consequently, no antibiotics currently have the approved indication of the prevention of postoperative endophthalmitis. While the results of the ESCRS Endophthalmitis Study has prompted many surgeons in Europe to use intracameral cefuroxime at the conclusion of a case, American cataract surgeons have not embraced the use of this intracameral antibiotic. However, 54% of respondents to a survey of members of the American Society of Cataract and Refractive Surgeons (ASCRS) said they thought it was important to have a commercially available broad-spectrum antibiotic formulated for direct intracameral injection and almost 82% said they would use or consider using such a product if it were approved and available in the U.S.[12]

Because endophthalmitis rates are extremely low, smaller studies often have insufficient power to detect differences between various treatments and techniques. In addition, the rapid evolution of cataract surgical techniques makes it difficult for the published literature to remain current with many common practices.

Etiology

The normal ocular surface is colonized with a spectrum of bacteria that are considered to be a primary source of infection in endophthalmitis.[13] Conditions altering the normal flora such as contact lens wear, blepharitis, lacrimal system disease, and previous ocular surgery may increase the risk for postoperative endophthalmitis.[13–15] The normal flora may also be altered in patients who are chronically institutionalized, health-care workers, and patients with indwelling catheters or with ileostomies or colostomies.[16] In a study reported in 2009, Hori et al.[17] obtained conjunctival swabs from 200 eyes about to have cataract surgery and found 163 (81.5%) had positive bacterial growth: 49.4% were *Propionibacterium acnes*; 24.7% coagulase-negative *Staphylococcus* (CNS), including 36 methicillin-sensitive CNS and 22 methicillin-resistant CNS; 4.3% *Staphylococcus aureus*, including 6 methicillin-sensitive *S aureus* and 4 methicillin-resistant *S aureus* (MRSA); and 12.3% *Corynebacterium*. Approximately 40% of *Staphylococcus* (37.9% CNS and 40.0% *S aureus*) was methicillin resistant. Furthermore, 18 of the methicillin-resistant CNS and all 4 MRSA were fluoroquinolone resistant.

Given the preponderance on the conjunctival surface, it is no surprise that gram-positive bacteria are the most common cause of postoperative endophthalmitis.[9,18–20] However, the prevalence of certain pathogens may vary by geographic region. According to the EVS, 94.2% of culture-positive endophthalmitis cases involved gram-positive bacteria; 70.0% of isolates were gram-positive CNS, 9.9% were *S aureus*, 9.0% were *Streptococcus* species, 2.2% were *Enterococcus* species, and 3.0% were other gram-positive species. Gram-negative species were involved in 5.9% of cases.[9] In contrast, a survey from India reported that gram-positive bacteria accounted for only 53% of postoperative endophthalmitis cases; 26% were gram-negative isolates and 17% were fungal.[21]

Evidence suggests that the incidence of MRSA ocular infections is rising, both in total numbers and as a percentage of all *S aureus* infections.[22–24] In the EVS, *S aureus* was the second most common organism after CNS. Major et al.[24] found that MRSA accounted for 44% of post-cataract *S aureus* endophthalmitis in one institution from 1995 through 2008, whereas not a single case of MRSA had been identified at the same institution from 1984 through 1992. A significant proportion of *S aureus* cases were resistant not only to methicillin, but also to the commonly used fourth-generation fluoroquinolones. All isolates were sensitive to vancomycin, the intravitreal antibiotic of choice to treat gram-positive bacterial infections.[25]

Risk Factors

Because bacterial isolates in culture-positive cases of endophthalmitis are also found on the ocular surface in 67% to 82% of patients with endophthalmitis,[18,26,27] the primary risk factor for endophthalmitis seems to be increased intraocular exposure to the patient's own normal adnexal and ocular surface flora. Increased surgical complexity and complications such as posterior capsule rupture and vitreous loss increase the risk for endophthalmitis.[7,26] Hatch et al.[7] reported a nearly 10-fold increase in the risk for endophthalmitis when an unplanned anterior vitrectomy is performed. Sutureless clear corneal incisions have been implicated as a risk factor for endophthalmitis in several studies.[11,28–30] Poor sterile technique increases the risk for endophthalmitis,[31] as do preexisting periocular infections and immunocompromised status.[26,32,33] Despite the increased surgical time required for trainees, a few recent studies suggest that cataract surgery by residents does not increase the risk for endophthalmitis.[34,35]

Immediate Sequential (Same Day) Bilateral Cataract Surgery

The practice of operating on both eyes sequentially during the same surgical session has always been

controversial, especially in light of the potential for bilateral blinding complications such as infectious endophthalmitis. Improved cataract surgical outcomes and shortened recovery periods have led to an increase in this practice, particularly in health-care systems with long waiting times for cataract surgery in the second eye. Collectively, the literature for immediate sequential bilateral phacoemulsification is reassuring with respect to the low risk for endophthalmitis when well-designed aseptic protocols have been followed.[36–44] In most of these studies, the second eye is treated as though it were from a new patient, with separate draping, gowns, gloves, instrumentation, medications, and disposable supplies. Nevertheless, anecdotal cases of bilateral endophthalmitis have been reported, and the true risk is difficult to ascertain.[45–47]

PREVENTION

Operating Room Aseptic Protocols

Hand Disinfection   As a hand wash, the combination of povidone–iodine 10% with a detergent remains the compound of choice for effective skin antisepsis. In vitro and in vivo tests show consistent bacterial kill rates of over 99.99%.[48,49] In the event of iodine allergy, chlorhexidine gluconate is an iodine-free antimicrobial that is as effective as povidone–iodine in bacterial suspension tests, although under practical conditions it may perform slightly less well.[50]

Operative Site Antisepsis

Practice patterns for the prevention of postoperative endophthalmitis almost universally include preoperative sterile preparation of the surgical site.[A] In most cases, this involves the instillation of povidone–iodine 5% into the conjunctival sac, a practice of proven efficacy in reducing the bacterial load (complete elimination of bacteria from the conjunctival sac is difficult).[51,52] In a recent European survey,[53] 99.5% of surgeons were using povidone–iodine irrigation for prophylaxis. However, this practice is by no means universal; a recent survey of ophthalmologists in Yemen[54] revealed that fewer than 6% routinely used povidone–iodine preoperatively despite its generally accepted effectiveness.[55–59] A recent prospective study demonstrated that topical moxifloxacin 0.5% had no significant additive effect on the preoperative reduction of conjunctival bacterial colonization beyond the effect of povidone–iodine 5% alone.[60] A 5% concentration of povidone-iodine is more effective than 1% in decreasing the human conjunctival bacterial flora in vivo.[61] There is some evidence that the use of lidocaine gel prior to instillation of povidone–iodine 5% diminishes its antimicrobial effect.[62]

In cases of documented or suspected iodine allergy, polyhexanide[63] or chlorhexidine gluconate are recommended as effective and well-tolerated alternatives. Recently, time-kill results for a linalool-hinokitiol-based eyelid skin cleanser proved superior to povidone–iodine 10% against *S aureus* and MRSA.[64]

While bacteria may gain intraocular access during surgery,[65,66] it has been demonstrated that povidone–iodine conjunctival irrigation effectively prevents intracameral contamination during phacoemulsification.[67] An evidence-based assessment of endophthalmitis prophylaxis found that preoperative povidone–iodine antisepsis received the highest rating and was the only measure that gained a "B" grade (meaning moderately important to clinical outcome).[31]

Draping and Lashes

The potential for microbial contamination from exposed lid margins and lashes seems clear. Although surgical trainees consider draping the eyelids to be one of the easiest components of cataract surgery, their proficiency in this task has not been reported.[68] Proper draping ensures that the lashes and lid margins are entirely sequestered by overhanging wraparound flaps from the drape, which are held in place by the speculum.[69–71]

Antimicrobial Agents and Resistance

Unfortunately, antibiotic resistance often develops rapidly. Causative factors include the widespread systemic use of antibiotics and the use of antibiotics in animal feed.[72,73] The emergence of resistant bacteria in ophthalmology has been documented in the evaluation of isolates from keratitis and conjunctivitis.[74,75] While newer fourth-generation fluoroquinolones theoretically have less susceptibility to the development of resistance and an enhanced spectrum of activity against many gram-positive bacteria,[76] the majority of MRSA bacteria are resistant to ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin.[77] The rapid evolution of resistant bacteria has amplified the importance of developing newer and more potent ophthalmic antibiotics. Besifloxacin, a new broad-spectrum fluoroquinolone, was recently approved for ophthalmic use. A potential advantage of this medication is that it has no systemic, veterinary, or agricultural uses.[78]

Cefuroxime, a second-generation cephalosporin with bactericidal action, was extensively evaluated in Sweden prior to its widespread use following the ESCRS Endophthalmitis Study.[79,80] One potential gap in the coverage of cefuroxime is multiresistant *Enterococci*. Although uncommon, endophthalmitis due to this pathogen carries a poor prognosis.

Vancomycin has also been used as an intracameral antibiotic for the prevention of endophthalmitis. Because vancomycin remains one of the last resorts in the treatment of multidrug-resistant bacteria, there has been controversy and historical concern about whether routine intracameral vancomycin administration could contribute to future resistance to the drug. Vancomycin may be the initial drug of choice for suspected exogenous bacterial endophthalmitis, severe bacterial keratitis, and orbital cellulitis.[81]

Topical Prophylaxis

In addition to preoperative povidone–iodine antisepsis,[82–84] perioperative topical antibiotic prophylaxis is very common in the U.S. However, controversy regarding its efficacy remains.[31,85] Fourth-generation fluoroquinolones have emerged as the most commonly prescribed topical prophylactic therapeutics because of their broad spectrum activity and superior ocular penetration.[12,86,87]

The optimal timing and frequency of topical antibiotic prophylaxis has also been the subject of debate. Many surgeons begin dosing fourth-generation fluoroquinolones on the day of surgery. However, based on the pharmacokinetics of these drugs, starting 1 to 3 days before surgery may be advantageous.[88] There is evidence that frequent instillation of topical fluoroquinolones immediately before surgery may increase the concentration of drug in the anterior chamber and decrease the bacterial load.[89,90] Preoperative topical antibiotic use reduces the number of bacteria on the ocular surface at the time of surgery; postoperative topical antibiotic use without a taper until the wound is sealed addresses postoperative inoculation.[91] It is common for antibiotic drops to be discontinued 1 week after surgery, although some literature suggests that the average time of presentation of endophthalmitis is 9.3 days after cataract surgery.[87] Further studies are needed to evaluate the ideal drug, dosing, and route to prevent postoperative endophthalmitis.

Intracameral Antibiotic Agents

Of the various methods of antibiotic prophylaxis, the strongest evidence supports a direct intracameral bolus at the conclusion of surgery. Two early and large retrospective studies suggested that direct intracameral injections of gentamicin and vancomycin were efficacious.[92,93] A 2002 retrospective study of direct intracameral cefuroxime injection in more than 32 000 cases in Sweden reported an endophthalmitis rate of 0.06%, which was significantly lower than comparable published rates.[79] Twelve of the 13 culture-positive endophthalmitis organisms were cefuroxime resistant, suggesting that this method of administration was

protective against organisms sensitive to the drug. Four additional European retrospective studies demonstrated statistically lower endophthalmitis rates using intracameral cefuroxime or cefazolin compared with using no intracameral antibiotic.[94–97] An approximately 10-fold reduction in endophthalmitis was reported in 3 of these studies.[94,95,97] One study suggested that cefuroxime was more effective when injected intracamerally than subconjunctivally.[96] Finally, a 3-year prospective nonrandomized study of more than 225 000 cases in Sweden found a lower rate of endophthalmitis with intracameral cefuroxime than with topical antibiotic use alone.[98]

The landmark multicenter prospective randomized study conducted by the ESCRS enrolled 16 603 patients and provides the strongest support for the efficacy of intracameral antibiotic prophylaxis.[11] The rates of culture-proven endophthalmitis were 0.050% and 0.025% in the 2 groups receiving intracameral cefuroxime prophylaxis compared with 0.226% and 0.176% in the 2 groups not receiving intracameral prophylaxis. Overall, direct intracameral cefuroxime injections resulted in a 5.86-fold decrease (95% confidence interval [CI], 1.72-20.0) in the risk for culture-positive endophthalmitis.[11,99]

Subsequently, one university eye hospital in Spain reported a significant decrease in postoperative endophthalmitis following routine adoption of intracameral cefuroxime prophylaxis based on the results of the ESCRS randomized study.[97] There was a statistically significant decrease in the post-cataract endophthalmitis rate between the period before (0.590%; 95% CI, 0.50%-0.70%) and after (0.043%; 95% CI, 0.002%-0.06%) routine intracameral cefuroxime prophylaxis was initiated at the hospital.

No comparative studies suggest the optimal antibiotic agent for intracameral endophthalmitis prophylaxis. The peer-reviewed literature generally supports the safety of using intracameral preparations of vancomycin, moxifloxacin, and several cephalosporins.[80,93,100–104] However, both TASS and dosing errors are acknowledged risks of compounding medications for intraocular administration.[105] One study concluded that intracameral cefuroxime was more cost effective than topical fluoroquinolones.[106] Others have suggested that moxifloxacin has theoretical advantages for intracameral prophylaxis because of its potency and bactericidal activity and because the self-preserved commercial formulation avoids the need for compounding.[86] In the only study of its kind,[107] one group used serial aqueous taps following cataract surgery to show that a single intracameral injection of vancomycin 1.0 mg achieved an aqueous drug concentration that was 4 times the minimum inhibitory concentration for most gram-positive bacteria for longer than 24 hours.

Finally, no good evidence exists to support mixing antibiotics into the irrigating infusion bottle as a method of intracameral prophylaxis. In the 2007 ASCRS survey,[12] approximately one-half the surgeons administering an intraocular antibiotic injected a bolus directly into the anterior chamber, whereas the other half added the drug to the infusion bottle. In light of the published evidence, the latter practice cannot be recommended.

Toxic Anterior Segment Syndrome and Intracameral Antibiotic Agents

Toxic anterior segment syndrome is an acute sterile postoperative inflammation that can occur after uncomplicated or complicated cataract surgery and typically presents within 12 to 48 hours of surgery. While problems with the cleaning and sterilization of instruments remains the most common risk factor associated with TASS, improper preparation of antibiotics for intracameral injection may also lead to inaccuracies leading to TASS. Toxic anterior segment syndrome has been associated with the use of intracameral antibiotics in a small number of cases.[108]

To reduce the risk for TASS, intracameral medications must be preservative free and have the proper concentration, pH, osmolarity, and osmolality. With specific regard to cefuroxime, the recommended dose of 1.0 mg in 0.1 mL has been shown to be welltolerated and cause no ocular toxicity.[80] Because of a misunderstanding in the dilution protocol, an outbreak of TASS was reported following the intracameral injection of cefuroxime mixed to deliver a dose almost 50 times higher than usual. The patients had significant postoperative inflammation of the anterior segment of the eye, with extensive macular edema.[109] Even following a strict dilution protocol under the controlled conditions of a research study, accurate dosage cannot be assured.[105]

The lack of a commercially available U.S. Food and Drug Administration–approved antibiotic preparation for intracameral use means that intracameral antibiotics must be mixed by the surgeon, the operating room nursing staff, or a compounding pharmacy. A 2007 ASCRS survey,[12] performed 8 months after the preliminary report of the ESCRS study, found that 77% of the more than 1300 respondents were not using intracameral antibiotics. However, 82% stated that they would likely adopt this practice if a reasonably priced commercial preparation were available. Fortyfive percent of the respondents not using intracameral antibiotic prophylaxis expressed concerns about the risk of injecting noncommercially prepared solutions. The survey determined that most respondents were using topical gatifloxacin or moxifloxacin (81%) and

were initiating topical prophylaxis at least 1 day preoperatively (78%) and immediately postoperatively (66%). Because its control group did not mirror these practices, the ESCRS study was not able to determine whether intracameral cefuroxime was equal to, superior to, or of adjunctive benefit to the most commonly used topical antibiotic protocols preferred by the ASCRS survey population. The development, clinical investigation, and regulatory approval of a commercially available antibiotic for intracameral use would help eliminate potential toxicity problems.[110]

Subconjunctival Injection

In the 2007 ASCRS survey,[12] only 13% of respondents were using subconjunctival antibiotic prophylaxis. Other recent surveys show considerable geographic variability, from 11% (Canada) to 42% (United Kingdom).[111,112] Although there are no prospective randomized studies to support the use of subconjunctival antibiotic prophylaxis, some clinical evidence suggests a protective benefit. Retrospective studies from Canada,[113] the U.K.,[114] and Western Australia[115] found statistically lower rates of endophthalmitis when subconjunctival antibiotics were given. The largest of these studies (Western Australia) was a population-based case-control study covering 1980 to 2000.[115] However, because most of the surgeons used topical antibiotics and did not use intracameral antibiotics, there was insufficient statistical power to assess the relative benefits of these methods of antibiotic prophylaxis. One study directly compared intracameral and subconjunctival cefuroxime in a retrospective study of nearly 37 000 cases at a single eye hospital and found the intracameral route to be statistically superior.[96] Because of the potential for intraocular leakage and toxicity, subconjunctival aminoglycosides should be injected at an adequate distance from the cataract incision.[116]

Postoperative Patching and Shield

One comparative randomized prospective trial compared 4 groups: no cover versus a transparent shield for 4 hours, no cover versus an eye pad for 4 hours, or no cover versus an eye pad overnight.[117] The study found no significant between-group differences in pain, foreign-body sensation, tearing, and photophobia. Even when peribulbar anesthesia was used, the benefits remained unclear. Another prospective randomized controlled trial compared a combined eye pad and shield with a shield alone.[118] The primary outcome measures were corneal fluorescein staining, discomfort, diplopia, and mobility. The study found that moderate or severe corneal fluorescein staining on the first postoperative day was significantly more

common in the eye pad plus shield group (39%) than in the clear shield only group (19%) ($P<.01$). There was no significant difference in postoperative pain as measured by visual analogue scale or by categorical pain scale. Another prospective study looked for differences in microbial culture using lid and conjunctival swabs taken from 2 groups: one with a gauze mesh, a pad, and clear shield and the other with a clear shield only. There were no between-group differences in growth.[119]

Surgical Technique

Many surgical factors can influence the risk for intracameral bacterial inoculation during routine phacoemulsification. These include incision location, architecture and integrity, aseptic technique, avoidance of ocular surface contact with instruments and the intraocular lens (IOL), and the duration of surgery.

Wound Construction   Regardless of the incision type, any postoperative wound leak increases the risk for endophthalmitis. Wallin et al.[120] found that a wound leak on postoperative day 1 was associated with a 44-fold increase in the risk for postoperative endophthalmitis. Meanwhile, most of the debate surrounding wound construction has centered on the relative risk of scleral tunnel incision versus sutureless clear corneal incision. In their prospective randomized study of more than 12 000 cataract surgeries, Nagaki et al.[121] found an increased risk for postoperative endophthalmitis in patients who had temporal clear corneal incisions than in those who had superior sclerocorneal incisions. This study's findings supported the observations found in other retrospective case-control studies.[122,123] Taban et al.[2] further postulated that the overall increase in the rate of postoperative endophthalmitis observed since 1992 is related to the introduction and adoption of clear corneal incisions.

Several studies offer a hypothesis for how clear corneal incisions could increase the risk for postoperative endophthalmitis. They suggest that postoperative hypotony due to external manipulation and leakage can lead to wound gaping and inflow. In a laboratory model using human globes,[124] 4 of 7 eyes demonstrated ingress of India ink through 3.0 mm clear corneal incisions. In a clinical study of 8 patients,[125] the ingress of blood-tinged tears was observed when a cannula was used to apply external pressure to the posterior side of clear corneal incisions.[125] Other studies suggest that stepped incisions may be more resistant to postoperative hypotony and ingress of extraocular surface fluid.[126–128]

An important consideration in assessing the risk of clear corneal incisions is the variability in their construction. These wounds can vary in width, radial length, depth, location, angle, anterior and posterior thicknesses, shape, and entry point. Some have suggested that the shape of the incision is more important than the size with respect to being self-sealing.[129] There is also variance in the types of blades used for wound construction. Even if surgeons could create the same incision architecture consistently, wound manipulation during cataract surgery could introduce variability. Most large retrospective studies that have implicated clear corneal incisions as a risk factor for endophthalmitis have not characterized their architecture, which would probably not be uniform or standardized in large multicenter series. Femtosecond laser technology offers the potential to create even more precise clear corneal incisional architecture. Whether this might impact endophthalmitis risk would be worthy of future study.

In addition to wound construction, wound location has been examined as a possible risk factor. Investigators from the Bascom Palmer Eye Institute[1] observed that 86% of cases of postoperative endophthalmitis at their institution occurred in right eyes with incisions located inferotemporally, in closer proximity to the inferior lid margin and tear meniscus.

Other studies suggest that there is no increased risk for postoperative endophthalmitis with sutureless clear corneal incisions. In a retrospective study of postoperative endophthalmitis from 2000 to 2004, Miller et al.[1] found a relatively low overall rate of postoperative endophthalmitis and no statistically significant risk from clear corneal incisions. In a large retrospective report from the U.K.,[130] no significant increase in the rate of postoperative endophthalmitis was identified from 1996 to 2004, a period when there was a transition from scleral tunnel to clear corneal incisions. As mentioned previously, Ng et al.[115] found no relationship between wound type and postoperative endophthalmitis. The largest study looking at the endophthalmitis risk of clear corneal incisions was conducted as part of the National Cataract Registry in Sweden.[5] In that prospective study of 225 471 cataract surgeries, there was a slightly higher rate of postoperative endophthalmitis in eyes with clear corneal incisions (0.053%) than in those with scleral incisions (0.036%) but the difference did not reach statistical significance ($P=.14$). Of note, 99% of the patients in that study received an intracameral cefuroxime injection, whereas fewer than 5% received postoperative topical antibiotics.[5]

One rationale cited for using microcoaxial or microbiaxial phacoemulsification is the possibility that smaller incisions might reduce the risk for postoperative endophthalmitis. As with prophylactic antibiotics, the low incidence of infection makes it difficult to prove the superiority of one incision size over another in a prospective study. Furthermore, improperly

constructed incisions or those that are stretched by instrumentation may leak regardless of their width. Despite the controversy over endophthalmitis risk with clear corneal incisions, there is general agreement that a suture should be placed if the incision is not watertight at the conclusion of surgery.[131,132]

Cost-Effectiveness of Various Prophylactic Measures for Prevention of Postoperative Bacterial Endophthalmitis

Substantial costs are associated with endophthalmitis, arising from its treatment and any subsequent visual loss. The EVS demonstrated that its recommendations could result in substantial cost savings.[133,134] Sharifi et al.[106] established a model to evaluate the cost-effectiveness of antibiotic prophylaxis and indicated an advantage for intracameral cefuroxime. Their model suggested that intracameral cefuroxime was 9 to 18 times more cost-effective than gatifloxacin and moxifloxacin and 8 times more cost-effective than ciprofloxacin. However, this cost-effectiveness analysis did not take into account costs associated with pain, suffering, and loss of function. In addition, the authors assumed availability of cefuroxime in one multiuse vial for an average of 4 cases.[12,135] Infection prophylaxis guidelines vary, and some institutions may require individual-use vials of cefuroxime. The medicolegal costs associated with endophthalmitis were also not considered in this analysis.

A 2009 study at the Aravind Eye Hospitals in India[6] evaluated cost-effectiveness measures for the prevention of postoperative endophthalmitis and found that short-cycle steam sterilization, reusable gowns, gloves, surgical tubing, and solutions were cost-saving measures that did not lead to increased endophthalmitis rates. The study used preoperative and postoperative topical antibiotics and povidone–iodine preparation of the eye but did not include intracameral or subconjunctival antibiotics.

Current Practice Patterns for Prevention of Postoperative Bacterial Endophthalmitis

Practice patterns vary by country based partly on availability of modes of chemoprophylaxis. These may include preoperative and postoperative topical, intracameral, subconjunctival, and oral antibiotics and sterile preparation of the eye for surgery.[31,A]

In the U.S., the most common method of antibiotic chemoprophylaxis is topical fourth-generation fluoroquinolones prescribed 1 to 3 days preoperatively and resumed immediately postoperatively, according to a 2007 ASCRS member survey.[12] Of the 91% of ASCRS member surgeons using topical antibiotic prophylaxis at the time of cataract surgery, 81% used gatifloxacin or moxifloxacin and an additional 12% used ofloxacin, ciprofloxacin, or levofloxacin. Eighty-eight percent of surgeons began antibiotics 1 to 3 days preoperatively and 98% prescribed postoperative antibiotics. The preferred postoperative antibiotic drop regimen was topical antibiotic use for 1 week (73%). Of the 90% of surgeons who administered antibiotics at the conclusion of surgery, 83% used topical application, 15% used an intracameral injection, and 13% delivered antibiotics with subconjunctival injection. In addition, 30% of respondents used intracameral antibiotics; half used them in the irrigation fluid and half favored direct injection. Vancomycin was used by 61% of those using intracameral antibiotics, cephalosporins were used by 23%, and fluoroquinolones by 22%.

United Kingdom practice patterns for postoperative prevention of endophthalmitis differ from those in the U.S. in that a significantly greater percentage of surgeons favor intracameral antibiotics.[136] A 2009 survey of United Kingdom & Ireland Cataract and Refractive Surgeons members[136] indicated that 63% used intracameral antibiotics, with 55% using cefuroxime and 5% vancomycin. Almost none of the surgeons used preoperative antibiotic prophylaxis, whereas the majority did use postoperative antibiotic prophylaxis. The most commonly used postoperative topical drops were chloramphenicol and neomycin. Sixty-seven percent of the U.K. respondents not currently using intracameral antibiotics stated that they would use intracameral cefuroxime if it became commercially available.[136]

A significant change in European Union practice patterns took place following the report of the ESCRS multicenter study, which showed the efficacy of intracameral cefuroxime in preventing postoperative endophthalmitis.[11,99,136] Prior to the ESCRS study, most U.K. surgeons (66%) used subconjunctival cefuroxime whereas only 18% routinely administered intracameral antibiotics (cefuroxime 10%, vancomycin 8%).[137] It is important to note that fourth-generation fluoroquinolones are not commonly available in Europe, making direct comparison of effectiveness difficult. The clinical implications of the ESCRS study continue to be controversial.[11,12,136,138]

Two Spanish studies of practice patterns for prevention of postoperative endophthalmitis indicated the widespread use of povidone–iodine; postoperative topical antibiotics including ofloxacin, chloramphenicol and/or tobramycin; and the use of intracameral cefazolin.[94,95] Chemoprophylaxis in Sweden includes widespread use of intracameral cefuroxime, with no additional preoperative or postoperative antibiotics.[79]

An endophthalmitis study of practice patterns in Western Australia found that 80% of surgeons used

preoperative topical antibiotics and 95% used topical postoperative antibiotics.[115] Nearly 100% performed antiseptic preparation, 50% administered subconjunctival antibiotics, and only 1% used intracameral antibiotics.

Publications from China indicate use of povidone–iodine skin preparation, instillation of povidone–iodine on the ocular surface immediately prior to surgery, and the administration of subconjunctival gentamicin. Intracameral antibiotics were not used, and the use of postoperative topical antibiotics was not reported.[84,139]

In summary, practice patterns for the prevention of postoperative endophthalmitis vary widely. Surgeons in most countries use preoperative povidone–iodine. Preoperative and postoperative topical antibiotics and the use of subconjunctival and intracameral antibiotics are the other commonly used modes of prophylaxis.

Future Directions in the Prevention of Postoperative Endophthalmitis

Future directions in the prevention of postoperative endophthalmitis include new preparations of antibiotics, novel drug delivery systems, and modifications of IOLs.[140,141] A recent experimental study in Japan compared the use of hydrophilic acrylic IOLs as an antibiotic delivery system with intracameral antibiotics for endophthalmitis prevention.[140] Gatifloxacin and levofloxacin were the agents used and were delivered intracamerally or by IOL adsorption. Similar effects against bacterial proliferation were noted with both modes of fluoroquinolone administration.

A Brazilian pharmacology group evaluated a controlled-release subconjunctival delivery system for ciprofloxacin and triamcinolone.[141] The findings indicated that this novel system provided higher levels of intraocular ciprofloxacin than topically applied antibiotic in an experimental rabbit model. It was equally efficacious in the prevention of endophthalmitis in this model.

Another new technique for endophthalmitis prevention is the modification of IOLs to potentially decrease bacterial adherence. Huang et al.[142] used surface modification of silicone IOLs by 2-methacryloyloxyethyl phosphoryl-chlorine binding, which demonstrated reduced in vitro bacterial adherence and colonization of *Staphylococcus epidermidis*.

TREATMENT
Clinical Picture

Postoperative endophthalmitis presents as 2 distinct entities: early or acute endophthalmitis, occurring within a few days of the procedure, and chronic or delayed endophthalmitis, which can present several weeks after surgery with more subtle symptoms. The more virulent organisms (eg, gram-negative bacteria) are associated with the acute type and the less virulent (eg, *P acnes*), with the delayed presentation.[32]

Patients with acute postoperative endophthalmitis typically present within 2 weeks of surgery with progressive pain, reduced vision, eyelid edema, conjunctival injection, and chemosis.[20,32,33] Patients often report sudden decrease of vision, aching pain, and severe photosensitivity. Because early intervention can save vision, telephone staff should be aware of these symptoms in postoperative patients to help speed triage, evaluation, and treatment.

Physical findings of acute endophthalmitis are usually not subtle. Patients present with anterior chamber inflammation ranging from excessive cell and flare to severe inflammation with fibrin and hypopyon. The presence of vitreous cells is characteristic. Patients who present with acute anterior segment inflammation and no vitritis, especially in the first 24 to 48 hours following surgery, may be more likely to have TASS than endophthalmitis.[10] The decline in vision from acute endophthalmitis is associated with corneal edema, anterior and posterior chamber inflammation, retinal vasculitis, hemorrhage, and inflammation.[32,33,143,144] More severe infections are correlated with loss of the red reflex and less than hand motion vision.[32] Infected eyes may have corneal infiltrates and leading wounds with fibrin tracking into the anterior chamber.

Chronic delayed-onset endophthalmitis is less common, and the symptoms and findings can be subtle.[32,145] Patients with chronic endophthalmitis may report only mild pain and photosensitivity that may be masked by postoperative corticosteroids. Al-Mezaine et al.[145] found an average delay of more than 5 months from surgery to the time of diagnosis. On examination, these patients may have only rare cellular reaction in the anterior chamber and vitreous and will rarely have keratic precipitates. They sometimes have white plaques on the IOL surface, haptics, or capsule. It is important to rule out retained lens material, which can cause persistent inflammation that mimics chronic endophthalmitis.

Diagnosis and Treatment

The differential diagnosis of acute severe inflammation in the immediate postoperative period includes infection, TASS, surgical trauma, retained lens fragments, and uveitic syndromes. Although the clinical distinction between these conditions can be difficult, infection must be ruled out because severe vision

loss of vision can result from even a slight delay in treatment. The differential diagnosis of chronic postoperative endophthalmitis includes endogenous infection and masquerade syndromes.[146]

Acute Endophthalmitis

Ideally, treatment of acute postoperative infectious endophthalmitis is both immediate and tailored to the specific antibiotic sensitivities of the organism involved. However, although symptoms and findings may correlate with the severity of the infection, they do not allow one to differentiate among infectious organisms.[147] Broad-spectrum antibiotics should be used because of the wide range of potential causative organisms and the requisite delay in obtaining culture results.

As established by the EVS, initial treatment of post-cataract-surgery endophthalmitis is 2-fold: specimen collection and antibiotic administration. A vitreous specimen is preferred as this roughly doubles the diagnostic yield compared with the aqueous (54.9% versus 22.5%).[148] Blood culture media appears to have the most successful yield at diagnosis when a small isolated specimen is obtained.[149,B] If the technique for biopsy is a 2-port or 3-port vitrectomy, the infusion line can be attached to a filter, with the filter then cultured. Culture media include chocolate and Sabouraud dextrose agar and thioglycolate liquid. Gram staining may help identify an infection and classify the organism, but a negative gram stain correlates poorly with the results of culture.[148]

The EVS concluded that the choice of vitreous tap or biopsy versus 3-port vitrectomy should be based on the presenting visual acuity.[9] In patients with visual acuity better than light perception, either method can be used without a clinical difference in the final outcome; however, in patients with light perception vision, a 3-port pars plana vitrectomy should be used because this regimen has demonstrated a 3-fold increase in the likelihood of 20/40 final acuity. The choice of vitreous tap versus vitrectomy does not increase the yield of the culture.[148] Regardless of the presenting visual acuity, diabetic patients present a special situation and have a greater likelihood of achieving a 20/40 acuity with vitrectomy (57%) than with a simple tap or biopsy (40%).[150] The most favorable prognosis for visual acuity is associated with coagulase-negative gram-positive cocci.[151]

Polymerase chain reaction (PCR) is a powerful diagnostic tool that can increase the yield of positive bacterial or fungal detection in aqueous and vitreous specimens when the diagnosis of infectious endophthalmitis is suspected.[152] The yield of PCR is the same for aqueous or vitreous sampling,[152] allowing the diagnosis to be made with a safer and more easily performed aqueous tap.[153] Unlike microbial cultures, which may be falsely negative in a large number of cases, a negative PCR effectively rules out a microbial infection with a high degree of sensitivity and specificity.[154]

Administration of broad-spectrum antibiotics and dexamethasone into the vitreous cavity should follow specimen collection (Figure 1). Although adjunctive routes of antibiotic administration are used, there is no evidence that supplemental topical and subconjunctival[155] delivery of antibiotics are efficacious in treating endophthalmitis. Intravenous antibiotics have not been shown to change either the final visual acuity or media opacity in this setting.[9] Newer antibiotics, such as systemic fluoroquinolones, however, have not been tested for efficacy in a rigorous manner.[156,157]

Secondary considerations for endophthalmitis treatment include repairing a wound leak and excising any vitreous to the wound (vitreous wick).[158] Within the first week after treatment, additional procedures were needed in 10.5% of patients in the EVS study; most (38 of 44) were due to worsening inflammation.[159,160] The repeat positive culture rate in patients who had vitreous biopsy with intravitreal antibiotics was 71%. In contrast, it was 13% in patients who had an initial vitrectomy. Vitrectomy thus appears to have improved the effect of antibiotics in sterilizing the intraocular contents. Failure to sterilize the intraocular contents with antibiotics alone may have contributed to worse outcomes in the most severe cases.

By 1 year, 26.9% of patients had additional treatments for posterior capsule opacification, recurrent endophthalmitis, glaucoma, or retinal detachment.[161] The EVS demonstrated a lower rate of retinal detachment (8.3%) than had been previously reported, and this did not differ significantly between patients having vitreous tap/biopsy or vitrectomy.[160] Prior to the EVS, retinal detachment rates of 14% to 21% had been observed in eyes with endophthalmitis treated with vitrectomy, but these studies were retrospective, did not differentiate treatment based on the presenting severity, and were published more than 10 years prior to the EVS (1985 and 1983).[161,162]

A strong argument for immediate complete vitrectomy, including peeling of the internal limiting membrane and intracameral antibiotics, is advocated by Kuhn and Gini.[163] Part of their rationale is the reduction of iatrogenic risks for vitrectomy due to significant advances in technology compared with the time of the EVS (1990 to 1994). Support for Kuhn and Gini can be found in the EVS itself. This includes the need for patients with diabetes to have primary vitrectomy to achieve the optimum outcome, the high positive rate

Amphotericin B Intravitreal Injection (0.005 mg/0.1 cc)
        To 50 mg vial, add 10 cc of nonpreserved normal saline
        To 0.1 cc of this solution, add 9.9 cc of nonpreserved normal saline
        Final concentration = 0.005 mg/0.1 cc
        Protect from light

Amikacin Intravitreal Injection (400 μg/0.1 cc)
        To 0.8 cc of amikacin (500 mg/2 mL), add 9.2 cc of NaCl nonbacteriostatic to make
        10 cc containing 200 mg of amikacin (solution #1)
        To 0.2 cc of solution #1 (4.0 mg), add 0.8 cc of NaCl nonbacteriostatic to make
        1.0 cc containing 4.0 mg = 4000 μg
        Inject 0.1 cc of solution = 0.4 mg = 400 μg

Cefazolin Intravitreal Injection (2.25 mg/0.1 cc)
        To 500 mg vial of cefazolin, add 2.0 cc of sterile nonpreserved normal saline
        Dilute 1.0 cc of this solution with 9.0 cc of normal saline, giving 10.0 cc total volume
        Final concentration = 2.25 mg/0.1 cc
        Inject 0.1 cc of solution = 2.25 mg

Ceftazidime Intravitreal Injection (2.25 mg/0.1 cc)—Use Fortaz (no other formulation)
        To 500 mg vial of ceftazidime, add 2.0 cc of sterile nonpreserved normal saline
        Dilute 1.0 cc of this solution with 9.0 cc of normal saline, giving 10.0 cc of total volume
        Final concentration = 2.25 mg/0.1 cc
        Inject 0.1 cc of solution = 2.25 mg

Decadron Intravitreal Injection (100 μg/0.1 cc)
        Withdraw 1.0 cc of Decadron (MSD brand only) 4.0 mg/cc
        Withdraw 3.0 cc of normal saline without preservatives
        Final concentration = 4.0 mg/4.0 cc (1.0 mg/1.0 cc)
        Inject 0.1 cc of solution = 0.1 mg = 100 μg

Gentamicin Intravitreal Injection (100 μg/0.1 cc)
        Withdraw 0.1 cc from vial of 80 mg/2.0 cc of gentamicin injection
        Dilute with 3.9 cc of nonpreserved normal saline, giving 4.0 mg/4.0 cc
        Inject 0.1 cc of solution = 0.1 mg = 100 μg

Vancomycin Intravitreal Injection (1.0 mg/0.1 cc)
        Dilute 500 mg vial of vancomycin with 10 cc of nonpreserved 0.9% NaCl
        Withdraw 2.0 cc of this solution and dilute up to 10 cc with 0.9% NaCl (add 8.0 cc of 0.9% NaCl)
        Inject 0.1 cc of solution = 1.0 mg = 1000 μg

Mutamycin 0.4 mg/mL for Topical Intraocular Use
        Vertical flow hood using aseptic technique
        Reconstitute 5 mg vial mutamycin with 12.5 cc of sterile water for injection; resulting solution is 0.4 mg/mL
        Transfer 0.5 cc into TB syring and cap off; makes approximately 20 syringes
        Freeze and maintain storage at 10°F or lower (syringes frozen have a 90-day
        expiration). When dispensed to ASC, label for 24-hour expiration keep in refrigerator.

All preparations should be made under sterile hood with millipore filters. **All concentrations should be confirmed by pharmacist making preparation.** More than the needed volume should be sent to the operating room to allow sterile transfer. To increase accuracy, inject from the TB syringe from one volume to another, eliminating error caused by fluid in the needle hub. For example, inject from 0.3 cc to 0.2 cc. Use extreme caution not to confuse intravitreal with subconjunctival antibiotics that may have also been made up for case (will be higher concentration and usually injecting 0.5 cc).

Figure 1. Preparation of intravitreal antibiotic agents.

of reculture in the vitreous tap/biopsy group, the exclusion of the most severe cases of infection from the EVS, and the exclusion of patients having procedures other than cataract extraction.

Chronic Endophthalmitis

In chronic endophthalmitis, causative organisms tend to be normal cutaneous flora, including *Propionibacterium species*, *S epidermidis*, and fungal species, most commonly *Candida*.[9] The presentation may be from weeks to years after cataract surgery and can be masked by treatment with topical steroids.

Classically, the capsule will display a white plaque surrounding the sequestered organism.

Polymerase chain reaction is an expeditious method of detecting chronic endophthalmitis with a simple anterior chamber tap. In the absence of PCR, the plaque should be biopsied and cultured. Cases of suspected chronic endophthalmitis should be treated with vitrectomy and intracameral antibiotics irrigated into the capsular bag.[164] Only 50% of cases will respond completely to this conservative treatment[165] probably because of the slow growth curve of these organisms and that injected antibiotics fail to maintain

therapeutic concentrations for sufficient duration.[166] Capsulectomy and removal of the IOL may be required in the rest of the cases for complete microbial eradication.

OUTCOMES: MEDICOLEGAL CONSIDERATIONS

In 2006, the Ophthalmic Mutual Insurance Company (OMIC) of the American Academy of Ophthalmology[C] reported that during the preceding 20 years, endophthalmitis had accounted for 0.6% of claims frequency (150 out of 2559) and 5.0% of claims severity ($3 345 964 out of $63 191 199).[D] Cataract surgery accounts for 61% of all endophthalmitis claims; however, only 23% of cataract-related endophthalmitis cases have resulted in an indemnity payment. The OMIC attributes this differential to satisfactory informed consent, widespread use of prophylactic measures, and prompt diagnosis and treatment. Analysis of risk management in these cases reveals the relative importance of after-hours telephone access and accurate diagnosis. Other important risk management issues include thorough documentation, proper sterilization procedures, sufficient indications for the initial cataract surgery, and prompt follow-up or referral. Timely diagnosis and treatment of postoperative endophthalmitis ultimately depends on appropriate telephone triage, 24/7 physician coverage, and timely coordination of care.[E] Breakdowns in sterilization procedures should be disclosed to patients at the time of occurrence to facilitate surveillance and avoid allegations of concealment.[F]

CONCLUSIONS

Because of the potentially devastating complications of postsurgical endophthalmitis, infection prophylaxis, diagnosis, and treatment have been the subject of ongoing research and debate. Although it is fortunate that postsurgical endophthalmitis is rare, the low incidence also makes it virtually impossible to perform enough prospective randomized clinical trials to determine the most effective means of prophylaxis. Ophthalmologists must therefore exercise clinical judgment based on the best available published evidence, which we have summarized in this review.

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