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REVIEW

Current Perspectives of Prophylaxis and Management of Acute Infective Endophthalmitis

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ABSTRACT

Endophthalmitis is an intraocular inflammatory condition which may or may not be caused by infective agents. Noninfectious (sterile) endophthalmitis may be attributable to various causes including postoperative retained soft lens matter or toxicity following introduction of other agents into the eye. Infectious endophthalmitis is further subdivided into endogenous and exogenous. In endogenous endophthalmitis there is hematogenous spread of organisms from a distant source of infection whereas in exogenous endophthalmitis direct microbial inoculation may occur usually following ocular surgery or penetrating eye injury with or without intraocular foreign bodies. Acute infective endophthalmitis is usually exogenous induced by inoculation of pathogens following ocular surgery, open-globe injury and intravitreal injections. More infrequently the infective source is internal and septicemia spreads to the eye resulting in endogenous endophthalmitis. Several risk factors have been implicated including immunosuppression, ocular surface abnormalities, poor surgical wound construction, complicated cataract surgery with vitreous loss and certain types of intraocular lens. Comprehensive guidelines and recommendations on prophylaxis and monitoring of surgical cases have been proposed to minimize the risk of acute endophthalmitis. Early diagnosis and prompt management of infective endophthalmitis employing appropriately selected intravitreal antibiotics are essential to optimize visual outcome.

Keywords: Cataract; Endophthalmitis; Vitrectomy; Infection; Intravitreal antibiotics; Ophthalmology; Uveiti

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INTRODUCTION

Acute infective endophthalmitis is an inflammatory ocular condition usually caused by bacteria and more infrequently by fungi, or other parasites. This potentially devastating intraocular infection may arise either exogenously or endogenously. In exogenous endophthalmitis, the infective agents enter the eye through a breach in the globe, most commonly following intraocular surgery or injection, while penetrating eye injury and intraocular extension of infection originating from the cornea or a filtering bleb represent less common causes. In case the infective source is internal and septicemia spreads to the eye, endophthalmitis is endogenous. In this perspective, a comprehensive overview of infective endophthalmitis with emphasis on treatment trends and prophylaxis guidelines will be presented.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

EXOGENOUS ENDOPHTHALMITIS

Post-Cataract Endophthalmitis

Endophthalmitis is a rare but potentially blinding complication of cataract surgery. The incidence of acute-onset postoperative endophthalmitis has steadily declined over the years from 10% in the first half of twentieth century to 0.014–0.08% nowadays [1–10]. The availability of advanced technology, the adoption of refined surgical techniques and the use of intracameral cefuroxime at the end of the operation have meaningfully contributed to this notable reduction in endophthalmitis rate [1–10].

Most endophthalmitis cases present within the first or second week after cataract surgery complaining of reduced vision and ocular pain [8]. Other ocular signs include eyelid swelling, conjunctival injection and intraocular inflammation ranging from mild inflammation to severe panuveitis with hypopyon. The severity and the prognosis of intraocular endophthalmitis is associated with the virulence and inoculum size of the offending organism, the time to presentation and initiation of appropriate therapy and the patient's immune status [2, 11–13].

The microbial spectrum of post-cataract endophthalmitis includes Gram-positive bacteria, predominantly coagulase-negative staphylococci, *Staphylococcus aureus*, β-hemolytic streptococci, *S. pneumonia* and *Enterococcus faecalis*. More rarely infection can be caused by Gram-negative rods including haemophilus influenza and pseudomonas aeriginosa [5–9]. It is important to point out that visual prognosis is extremely guarded when virulent strains of streptococci or Gram-negative microbes are involved [2, 14, 15]. Bacteria causing endophthalmitis are summarized in Table 1.

Table 1 Bacterial causes of endophthalmitis

Gram positive	Coagulase-negative staphylococci
	Staphylococci aureus
	B-hemolytic streptococci
	S. pneumonia
	E. feacalis
Gram negative	*Haemophilus influenza*
	Pseudomonas aeriginosa

Risk Factors

Several risk factors for the development of acute post-cataract endophthalmitis have been suggested [1, 8, 10, 11, 16, 17]. They can be divided into preoperative, including diseased ocular surface, poor hygiene and systemic immunosuppression and intraoperative including poor surgical wound construction, complicated cataract surgery with vitreous loss, type of intraocular lens inserted, topical anesthesia, and prolonged surgical time [11, 16, 17]. The European Society of Cataract and Refractive Surgeons (ESCRS) multicentered study [1] evaluated the above parameters in a large cohort of over 16,000 patients undergoing phacoemulsification cataract surgery and identified 3 factors that significantly increase the risk of postoperative infectious endophthalmitis: a clear corneal incision (CCI), the use of silicone intraocular lens implants (IOLs) and the occurrence of surgical complications. In contrast, the use of intracameral Cefuroxime was associated with significantly reduced risk of postoperative endophthalmitis (Table 2).

Table 2 Risk factors for endophthalmitis identified in the ESCRS study [1]

Risk factor	Odds ratio
Intra-cameral injection of cefuroxime—given or not given	4.92
Clear cornea (and position) versus scleral tunnel incision	5.88
Type of wound closure	No evidence found
Insertion of IOL—injector or forceps	Not retained as a risk factor
Type of IOL material	3.13
Diabetic or non-diabetic	No evidence found
Immunosuppression or not	No evidence found
Equipment sterilization—disposable vs reusable	No evidence found
Complications of surgery	4.95

IOL intraocular lens

Historically, the popularization of sutureless CCIs coincided with a rise of endophthalmitis rate from 0.087% to 0.265% at the end of the previous century [4]. Taban et al. [8] in a large meta-analysis reported an increased risk of endophthalmitis when CCI as opposed to scleral tunnel technique was adopted and the ECSRS study prospectively confirmed those observations reporting that patients who underwent CCI procedure were 5.88 times more likely to present postoperatively with endophthalmitis [1]. Construction of the corneal tunnels, which are more prone to gapping allows exogenous microorganisms to gain easier access to the anterior chamber [1, 11]. However, refinement of corneal incision technique and the use of intracameral cefuroxime have recently been shown to significantly reduce this risk [18].

Implantation of silicone IOLs has also been associated with a threefold increase in the endophthalmitis rate compared to standard acrylic, or Poly(methyl methacrylate) intraocular lenses [19]. It has been postulated that this finding may be attributable to both the hydrophobic nature of silicone and the surface biofilms forming on the IOLs [1]. Finally, intraoperative complications, specifically capsular rupture and consequent vitreous loss has been identified as a consistent risk factor in several studies, increasing the incidence of endophthalmitis by 3–17 times [1, 20].

Prophylaxis

It has been demonstrated that ocular surface abnormalities including blepharitis, or other chronic eyelid or conjunctival inflammation is associated with increased microbial load [16]. While a positive culture does not directly translate into a direct risk of infectious endophthalmitis, these data suggest that it may be beneficial to look for and treat moderate to severe blepharitis prior to cataract surgery [4, 21–24]. The most effective method to ensure preoperative antisepsis, is application of providone–iodine 5–10% to the cornea, conjunctivalsac and periocular surface for a minimum of 3 min prior to ocular surgery. This results in a significant reduction (up to 90%) of the normal ocular surface flora and has been consistently shown to meaningfully reduce postoperative endophthalmitis rates [1, 4, 11, 16, 21, 24, 25]. Povidone–iodine application should be carried out after the removal of the anesthetic gel employed in cases of topical anesthesia, as the latter has been shown to avert povidone–iodine's access to conjunctival flora and potentially may increase the risk of endophthalmitis [26].

Several, mainly European-controlled studies, have reported that intracameral administration of antibiotics at the end of the surgery has a meaningful protective effect against the development of endophthalmitis [11, 19, 21, 27–29]. In the ESCRS study, patients underwent phacoemulsification cataract surgery and were divided into four treatment groups (povidone–iodine alone, or povidone–iodine plus an additional therapy—intracameral cefuroxime, topical levofloxacin, or both). Results showed that when intracameral cefuroxime (1 mg in 0.1 mL normal saline) was not used there was a 4.92-fold increase (95% confidence interval, 1.87–12.9) in the risk of postoperative endophthalmitis (Table 2). The same study demonstrated the preventive effect of perioperative topical administration of levofloxacin, which can achieve high concentration in the anterior chamber after topical application [1, 19]. However, no study has shown the superiority of preoperative topical antibiotic administration as opposed to the use of povidone–iodine alone. Moreover, the growing rates of antibiotic resistance represent an area of concern [11, 30].

Management

The mainstay of treatment for acute infectious endophthalmitis following cataract surgery remains the prompt injection of suitable intravitreal antibiotics combined with pars planavitrectomy (PPV) for the most severe cases. Collection of a vitreous specimen with vitrector or needle should always precede administration of antibiotics and the samples should be delivered to a forewarned microbiologist for Gram-stain culture and appropriate microbial sensitivity testing [2].

A combination of two intravitreal antibiotics is recommended to ensure sufficient coverage of both Gram-positive and Gram-negative organisms (Table 3). Vancomycin 1 mg and ceftazidime 2.25 mg are currently considered as the optimal first line therapy [19]. Alternatively, vancomycin can be used in conjunction with amicacin specifically in β-lactame sensitive patients. This regimen provides better synergetic effect but has lost popularity due to the increased probability of retinal toxicity [1, 2, 11, 31, 32]. For fungal endophthalmitis, amphotericin B 5 μg, or voriconazole 100 μg is recommended [34]. Repeat intravitreal antibiotic administration is performed after at least 48 h and the selection of regimen is guided by the response to the initial injection and the culture sensitivity results. Systemic antibiotic therapy with the same drugs used for intravitreal injections or oral fluorquinolones may be used as adjunctive

Table 3 Common intravitreal drugs used in the treatment of endophthalmitis

	Intravitreal agents	Intravitreal dose (μg/0.1 ml)	Type of endophthalmitis
First line therapy	Vancomycin	1000	Bacterial
	Ceftazidime	2225	
	Dexamethasone	400	
Alternatives	Amikacin	400	
	Cefuroxime	2000	
	Erythromycin	500	
	Gentamycin	200	
	Moxifloxacin	50–160	
	Clindamycin	1000	
First line therapy	Amphotericin B	5–10	Fungal
	Voriconazole	100	
Alternatives	Miconazole	5 or 10	

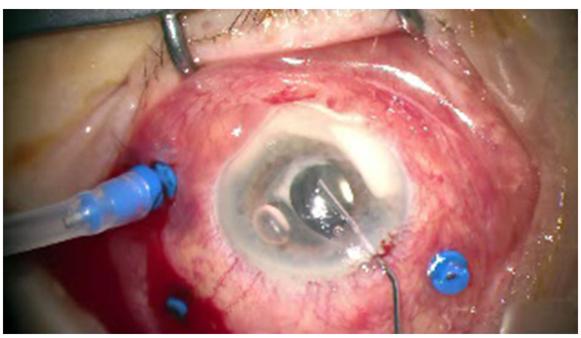

Fig. 1 Pars plana vitrectomy combined with anterior chamber wash out in a patient with acute post-cataract infective endophthalmitis

treatment to reach and maintain high intraocular concentrations [1, 11, 33, 34].

Although the Endophthalmitis Vitrectomy Study (EVS) recommended performing a pars plana vitrectomy only in patients presenting with visual acuity of Light Perception (LP), recent reports have demonstrated favorable functional and anatomical outcome even when surgical intervention was carried out in cases with better than LP visual acuity (Fig. 1). Prompt management and technical advances in vitrectomy are likely to account for these results [1, 35].

Cornea-Related Endophthalmitis

The incidence of endophthalmitis following penetrating keratoplasty ranges from 0.2% to 0.4% [36]. Wound dehiscence, suture abscess and the chronic use of topical steroids have been implicated as causative factors [37] (Fig. 2). The microorganism involved can be either bacterial (Gram-positive or Gram-negative species) or fungal (*Candida* species) [38–40]. Prolonged duration of cornea storage times have been associated with the development of fungal endophthalmitis [41]. Despite treatment (topical and intraocular antimicrobials, keratoplasty, pars planavitrectomy), the outcomes can be devastating with severe visual loss in more than 50% of cases [42].

Bacterial and fungal endophthalmitis have also been reported following endothelial keratoplasty [43]. Similarly, endophthalmitis

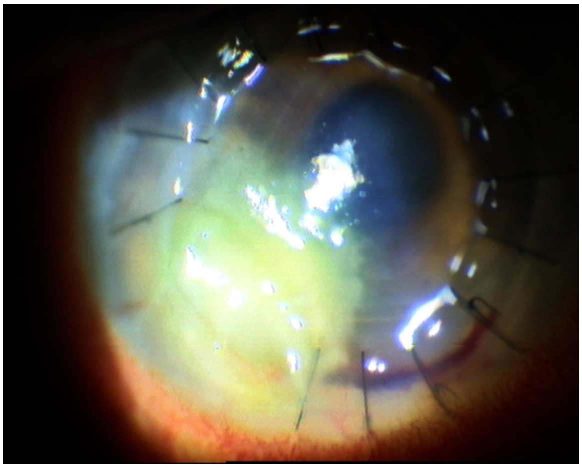

Fig. 2 Endophthalmitis associated with infected suture following penetrating keratoplasty. The suture was subsequently removed

can develop following keratoprosthesis (k-Pro) surgery with a reported incidence varying from 0% to 12.5% in the published literature [44–47]. Time from keratoprosthesis procedure to the onset of infection, ranges from 6 weeks to 46 months [48]. Diagnosis is usually challenging due to the development of retroprosthetic membrane and the limited aperture available for posterior segment examination [49]. The disease must be differentiated from sterile vitritis which typically presents with sudden onset of painless visual reduction accompanied by florid anterior chamber and vitreous reaction [44, 46]. In contrast with infectious endophthalmitis there is lack of tenderness or injection and the condition is highly responsive to intensive topical steroids, with frequently complete visual recovery. The microorganisms involved in infections are either Gram-positive cocci (the most common cause), Gram-negative organisms or fungi [48]. Topical antibiotics and soft contact lenses have been used for prophylaxis against endophthalmitis. Vitreous tap and injection of intravitreal antibiotics (vancomycin, ceftazidime) have been used for the treatment of post-k-pro endophthalmitis, however, good postoperative outcomes have also been reported with the use of 25-gauge pars planavitrectomy [11].

Progression of infectious keratitis to endophthalmitis is relatively uncommon (0.5%) [50–52]. Risk factors include age, dry eye, corneal perforation, fungal infection, systemic immune dysfunction, steroid use (topical and oral), dementia and nursing home care [50–52]. *Pseudomonas aeruginosa*, staphylococcus and streptococcus species are the most common bacterial causes [50] while aspergillus and fusarium species are less frequent [53]. Despite treatment visual outcomes are poor and often evisceration or enucleation is required [51, 52].

Endophthalmitis Associated with Vitreous Procedures

Endophthalmitis following pars plana vitrectomy is usually rare with the incidence ranging from 0.018% to 0.076% [54–59]. Following the introduction of small-gauge vitrectomy, concerns developed regarding an unexpected increase in the incidence of postoperative endophthalmitis [58, 60, 61]. However, review studies could not conclude that small-gauge vitrectomy is associated with higher risk of endophthalmitis [62–64], while two studies comparing endophthalmitis rates following 20-, 23- and 25-gauge vitrectomy failed to demonstrate any significant difference between the three groups [57, 65]. A higher incidence of endophthalmitis has been reported in fluid-filled eyes compared with air or gas filled eyes [66]. Posterior vitreous wick syndrome has also been proposed as a risk factor for postvitrectomy endophthalmitis [67]. Maintaining the infusion bottle at normal levels, removing herniated vitreous and avoiding high intraocular pressure at the end of the operation may prevent the occurrence of this syndrome, thus minimizing the risk of postvitrectomy endophthalmitis [58, 68]. Other risk factors associated with increased susceptibility to infection include the use of intravitreal, or topical corticosteroids [69, 70], the presence of immunosuppression, diabetes and older age [61, 70].

The Microsurgical Safety Task Force has provided suggestions to minimize the risk of post-PPV endophthalmitis [61] (Table 4).

The use of intravitreal antibiotics alone, or in combination with therapeutic vitrectomy has been used for the treatment of post-pars planavitrectomy endophthalmitis. Unfortunately, many cases have a poor visual outcome (vision worse than 20/200), nevertheless, occasionally better visual acuity (>20/40) may be possible [57, 71].

Postintravitreal Injection Endophthalmitis

The use of intravitreal injections represents one of the fastest growing fields in ophthalmology over the past decade. Considering that in 2008, approximately 1 million injections covered by Medicare were given in the United States, the estimated global number currently given in a year worldwide, may exceed 2 million injections [72]. Consequently, the reported prevalence of intravitreal injection-related endophthalmitis has also grown and it is now thought to be the second most common cause of endophthalmitis after cataract surgery [73]. This is especially important given that a patient may undergo many more intravitreal injections in a lifetime than cataract surgeries.

Epidemiology

The rate of endophthalmitis per intravitreal injection is low, with reported rates varying from 0.025% to 0.2% [74–76]. Given the rarity of infection and the effect that a single case can have on a data set, the range unsurprisingly has been wide. However, recent studies with large sample sizes have narrowed down the estimated rate to be between 0.02% and 0.03%. A study using a Medicare database of over 40,000 intravitreal injections found an endophthalmitis rate of 0.09% per injection [77]. A Boston study reviewed 10,208 injections that resulted in three infections, all of which were culture proven. This yields a rate of 0.029% per injection [78]. A review of the British Ophthalmological Surveillance unit found 47 cases in an estimated 186,972 injections, giving a per-injection rate of 0.025% [74]. The number of total injections in this study was extrapolated. These two studies note that the first infection occurred after the 7th and 5th injections, respectively, suggesting that the rate of infection is not affected by whether it is early or later on during the treatment course. A study from Miami documented 11 endophthalmitis cases in 60,322 injections, a rate of 0.02% [79]. Out of these data, a rate of approximately 0.7% chance

Table 4 Recommendations from the Microsurgical Safety Task Force [61]

Recommendations from the Microsurgical Safety Task Force
Eye preparation: 10% povidone–iodine
Wound construction: conjunctival displacement beveled or tapered incision
Case completion: tamponade, avoid vitreous incarceration, check intraocular pressure at the end of surgery
Postoperative: employ subconjunctival and topical antibiotics

of endophthalmitis has been derived for a patient undergoing a 24-injection course of treatment.

Microbiology

There are three possible sources of infection implicated in the injection-related endophthalmitis, including the normal ocular flora, the injection environment, and the clinical staff providing the injection. A study conducted in England reported 47 post-injection endophthalmitis cases, with 60% positive yield of the evaluated cultures [74], and more than 95% of them caused by Gram-positive bacteria [80]. Coagulase-negative staphylococci and *Viridians streptococci* were implicated in 60% and 25% of the cases, respectively [3, 80]. The above incidence of streptococcal endophthalmitis is considerably higher as opposed to post-cataract endophthalmitis (Fig. 3). *V. streptococci* was also the infective isolated agent in an outbreak of 12 post-injection endophthalmitis cases caused by contaminated Avastin syringes made up by a single compounding pharmacy [81]. Similar to those were the results of a recent meta-analysis, which examined the bacterial isolates from 26 cases, reporting that coagulase-negative staphylococcus was the cause of infection in 65.4% of cases and streptococcus species were implicated in 30.8% [82]. When compared, the microbiologic profile of injection-related infection cases and post-cataract infection cases was different in that a significantly higher rate of streptococcus infection was identified in the former group (24.53% vs 6.24%; $P = 0.022$) [3]. Considering this finding it has been postulated that contamination from oral flora may be the cause of the higher rates of streptococcus in intravitreal injections as compared to cataract surgery [82].

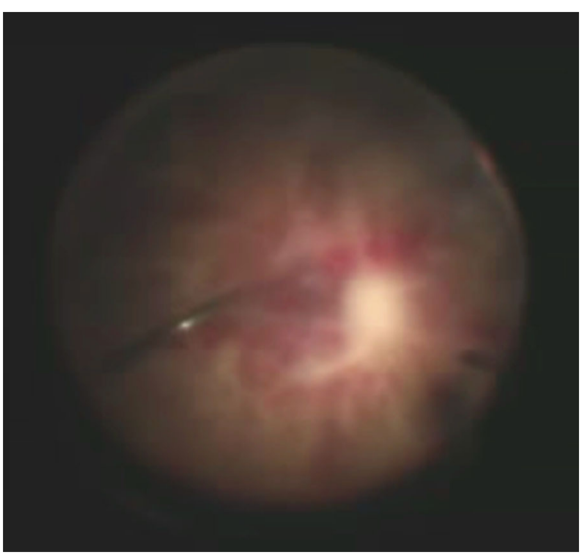

Fig. 3 Acute infective endophthalmitis of the right eye, caused by *Streptococcus viridians* 3 days following intravitreal injection. Extensive involvement of posterior segment is noted with diffuse retinal hemorrhages and profound exudation

Guidelines for Prophylaxis

Reported risk factors for postintravitreal injection endophthalmitis include old age, diabetes mellitus, blepharitis, subconjunctival anesthesia, patient's poor cooperation during injection and the use of compounded medication [83]. In 2014, an expert panel of retinal specialists updated the previously published guidelines on prophylaxis and monitoring of intravitreal injections. Part of the recommendations which were based on the existing literature referred to perioperative strategy to minimize the risk of acute postintravitreal injection endophthalmitis.

Importantly, eyelid, adnexal and ocular surface abnormalities should be considered as a potential risk factor for endophthalmitis since most endophthalmitis cases following intravitreal injections in patients with such abnormalities were attributed to *S. epidermidis* [84]. Therefore, eyes with active external infection should have the injection postponed until the infection is adequately managed. A prospective-controlled study confirmed this approach reporting that blepharitis was present in 6.5% of 47 postintravitreal injection endophthalmitis cases ($P = 0.006$) [74]. In general, patients undergoing intravitreal injections should meet the same hygiene considerations as those patients undergoing intraocular surgery a fact that is consistent with standards of good medical practice.

Povidone–iodine (5–10%) should be the last agent applied to the intended injection site and should be left in place for at least 30 s prior to the injection [85]. Povidone–iodine may also be applied gently to the eyelids, including the eyelid margins and eyelashes. However, it has been shown that eyelid scrubbing or eyelid pressure may dislodge bacteria from the accessory glands and therefore should be avoided. In case an anesthetic gel is used, povidone–iodine should be instilled both before and after the application of the anesthetic gel. Ocular surface preparation with povidone–iodine appears to be advantageous as compared with topical antibiotics, since it does not seem to promote bacterial resistance [86]. It has also been proposed that povidone–iodine flush is more effective in reducing bacterial population compared to a single drop application [87].

There is little scientific evidence to support that routine use of sterile gloves is associated with a reduced risk of endophthalmitis following intravitreal injections. Although there are no controlled data, the use of gloves is considered as a part of general infection avoidance clinical practice. In two prospective randomized controlled trials performed by the Diabetic Retinopathy Clinical Research Network, the use of gloves, or a drape was not essential and the endophthalmitis rate was relatively low (0.078%, 3 out of 3838 injections) [88]. An endophthalmitis rate of 0.057% was reported in a retrospective case series of 15,895 injections involving ranibizumab, bevacizumab, triamcinolone acetonide, and pegaptanib in which gloves were not used [89]. Despite the fact that the use of gloves is not strictly required by either evidence-based studies or regulations, this step is routinely adopted by the majority of physicians who find it consistent with good clinical practice. In a survey of 765 retina specialists, 58% reported use of gloves, and of those, 58% used sterile gloves [90]. Regardless of the use or nonuse of gloves, careful handwashing before and after patient contact and adhesion to aseptic injection technique is recommended for intravitreal injections.

Although the use of sterile drape is considered part of the routine preparation for major or minor operations, there is no body of literature to justify its use when performing routine intravitreal injections since studies failed to reveal an increased endophthalmitis rate when drape was not used [91]. Moreover, in nonophthalmic surgical procedures, a Cochrane meta-analysis showed that the use of plastic adhesive drape may even be harmful as it is related to a significant increase in local infections [92]. The rationale behind characterizing the use of drape unnecessary and problematic is further reinforced by its potential to upregulate patient's stress and discomfort [93].

The impact of wearing facial masks or minimizing talking during the procedure of injections has not been evaluated by randomised controlled trials. Nevertheless, current literature suggests that the notably high rate of streptococcus isolates implies that causative organisms are likely to be transmitted from oropharyngeal droplets [94, 95]. Previous studies confirmed that a procedure protocol involving use of a face mask and avoidance of talking is associated with a significant decrease in culture yield of plates positioned next to the mouth [96, 97]. Adopting such a policy should reduce the risk of endophthalmitis minimizing the spread of aerosolized droplets containing oral contaminants.

The eyelashes and the lid margins may represent primary source of infection because of needle contact during entry into the vitreous. Therefore, it is logical to prevent contact of the lids and lashes with the injection needle and ocular surface. Although the beneficial role of speculum has not been adequately confirmed by the current literature and despite patient discomfort that might generate, it should be considered as part of the optimized injection protocol, providing a more sterile environment and potentially minimizing the risk of endophthalmitis [98, 99].

The use of pre- or postintravitreal injection treatment with topical antibiotics has been the standard clinical practice for many years. However, several studies that evaluated their role, failed to demonstrate any significant benefit regarding endophthalmitis prevention. Moss et al. conducted a randomised controlled study showing that a 3-day course of gatifloxacin prior to injection did reduce the positive yield of conjunctival cultures, but there was no additional benefit in combination with povidone–iodine versus eyes that only received povidone–iodine. Similarly, other large retrospective studies did not demonstrate a clinical benefit for the use of topical antibiotics after an injection [100]. This is consistent with reports showing that following an injection, topical antibiotics fail to attain sufficient therapeutic levels within the vitreous cavity. The lack of benefit along with the potential for development of antibiotic resistance and concomitant cost, render perioperative use of antibiotics probably unnecessary.

Management

Similar to post-cataract endophthalmitis, the most common etiologic agent in injection-related endophthalmitis is coagulase-negative staphylococcus. Consequently, some clinicians have used the EVS recommendations to guide their treatment strategy. Although the ideal timing of vitrectomy remains as yet unclear, it is widely accepted that initial vitreous tap and antibiotic injection is a reasonable therapeutic approach. Vancomycin 1.0 mg/0.1 ml with either ceftazidime 2.25 mg/0.1 ml, or amikacin 0.4 mg/0.1 ml, remains the mainstay of current treatment. Subsequent injections should be tailored to culture results avoiding amikacin due to retinal toxicity [101].

Endophthalmitis associated with intravitreal injections can have variable outcomes depending on the virulence of the infective organisms. A large retrospective study of 27,736 injections showed that 78% of the 23 presumed infectious endophthalmitis cases regained baseline visual acuity. The authors reported no difference in the visual recovery rate based on positive or negative yield of cultures. Endophthalmitis patients following intravitreal injections exhibit worse prognosis compared to those post-cataract surgery. It has been postulated that is attributable to the increased incidence of *Streptococcus* spp. in the former group, or alternatively it may reflect differences in the ability of inoculated organisms to multiply in the vitreous as opposed to the anterior chamber [11].

Endophthalmitis after glaucoma surgery

One of the most dramatic complications after glaucoma filtering surgery is bleb-related endophthalmitis. The reported rate varies from 1.3%/patient/year for superior blebs to 7.8%/patient/year for inferior blebs [102–104]. It is critical to clearly differentiate between blebitis, which is an isolated bleb infection with varying degrees of anterior segment inflammation and bleb-associated endophthalmitis with coexisting vitreous involvement. Risk factors may include the use of antifibrotic agents (5-fluorouracil and mitomycin-C), chronic bleb leak, a thin avascular bleb, bleb manipulation, bacterial conjunctivitis and blepharitis, accidental minor trauma, epithelial drying, young age and male sex [105–109]. In late-onset endophthalmitis the microorganisms are often more virulent, with streptococcus species implicated in nearly 50% of these cases, compared to coagulase-negative staphylococcus, which is the most common pathogen in the early postoperative endophthalmitis [11, 110]. Treatment of bleb-associated endophthalmitis includes vancomycin, or amikacin (as topical eye-drops and intravitreal injections), oral fluoroquinolone, and topical corticosteroids [111–115]. PPV is likely to be required given the aggressive organisms involved and the extremely poor visual outcomes anticipated [110]. The Tube versus Trabeculectomy Study observed that the occurrence of endophthalmitis, or blebitis were more frequent in the trabeculectomy group compared to the tube group. This result raises concern, but the power of that study was limited with regard to identifying rare complications [116].

Late endophthalmitis may also develop after valve implantation as mentioned before. Insufficient conjunctival coverage and exposure of the device increase the risk. Immediate treatment with topical antibiotics and scheduling of a new surgery to cover the implant is essential [117].

Endophthalmitis Secondary to Trauma

The frequency of post-traumatic endophthalmitis following open-globe injuries (Figs. 3, 4) varies among different studies between 1% and 18.9% [118–122]. The development of infection can be acute, or delayed while risk factors identified include delayed presentation for eye examination, worse visual acuity at presentation, the presence of intraocular foreign body and the species of microorganisms involved [119, 123–125]. Especially for trauma cases associated with the presence of intraocular foreign bodies, the risk of endophthalmitis depends on the size and composition of the foreign body, the presence of contaminating materials such as soil, the speed of the foreign body, the path within the eye, the length of time between injury and removal of foreign body, the state of the immune system of the patient and the treatment regimen undertaken [125].

Fig. 4 Endophthalmitis associated with penetrating eye injury. Note the presence of hypopyon and the subconjunctival hemorrhage at the entry site

Staphylococcus and streptococcus species have been most frequently identified in post-traumatic endophthalmitis cases [34, 126]. *P. aeruginosa* and bacillus cereus are also frequently identified but their prevalence varies with geographic location [120, 127]. Bacillus species are associated with worse prognosis as they can cause visual loss and destruction of ocular tissue even within hours after the injury [128, 129]. Fungi species have been also isolated in a small percentage of post-traumatic endophthalmitis [124, 130].

The use of systemic and intraocular antibiotics for prophylaxis against post-traumatic endophthalmitis remains controversial. Nevertheless, when systemic antibiotics are not employed after open-globe injuries there is a greater risk for endophthalmitis development [131, 132]. In a prospective, randomized study, cases of intraocular foreign bodies that have been managed with intracameral and intravitreal antibiotics have been associated with a reduced risk of endophthalmitis compared with the control group treated with intravitreal balanced salt solution [133].

Treatment in post-traumatic endophthalmitis should be aggressive, with vitrectomy combined with intravitreal antibiotics (e.g. vancomycin plus ceftazidime) and systemic antibiotic therapy. Topical and subconjunctival antibiotics can also be used. However, the optimal primary closure of an open-globe injury remains an essential step to improve the prognosis of these challenging cases [134, 135].

Endogenous Endophthalmitis

Endogenous endophthalmitis develops when microorganisms that originate from an obvious (e.g. pneumonia, meningitis, endocarditis, hepatic abscess) or, more rarely, a non-obvious (e.g. osteomyelitis, sinusitis) extra-ocular septic focus gain access to the eye via the blood stream [136, 137]. This is usually associated with the presence of systemic risk factors, although rarely it can develop in the absence of concomitant risk factors [138]. Well-known risk factors include diabetes mellitus, malignancies, intravenous drug abuse, systemic lupus erythematosus, endoscopy, chemotherapy, acquired immune deficiency syndrome, sickle-cell anemia, dental procedures, and other immunocompromised states [73, 139].

Endogenous bacterial endophthalmitis is responsible for less than 10% of endophthalmitis cases [140]. Gram-positive (*S. pneumoniaes, aureus*, *Bacillus cereus*) and Gram-negative microorganisms (*Neisseria meningitidis*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae*) have been isolated in these rare cases [138–143].

Apart from the ocular findings suggestive of endophthalmitis, systemic symptoms and signs including fever and malaise. Further, positive blood cultures may be elicited in these cases. Retinal detachment, cataract, perivascular hemorrhages, low intraocular pressure and phthisis, sepsis and death can develop during the course of the disease. Prognosis depends on the general state of health of the patient [139, 140].

Endogenous fungal infections are less common than endogenous bacterial endophthalmitis and are usually caused by *Candida albicans*, *C. grabrata* [144, 145]. It is well documented that when immunosuppression co-exists, many organs, including the eye, can be affected. The infection presents either with visual loss (macular involvement), or with ocular pain (anterior uveitis, scleritis). Retinal foci less than 1 mm in diameter can become coalescent and develop into a mushroom-shaped lesion, which projects to the vitreous body. Furthermore, typical findings include the appearance of fluffy white vitreous opacities, described as a "string of pearls" appearance [146]. A second etiological agent is aspergillus (fumigatus, flavus) which is found in the loam (soil) and produces large choroidal infiltrates, subretinal hypopyon, retinal necrosis, vitreous exudates and vasculitis [147]. Intraocular infection caused by fungi can possibly present as masquerade syndrome and be treated erroneously with corticosteroids, which will aggravate the disease and negatively impact prognosis. Macular involvement is associated with poor prognosis with final visual acuity less than 20/200 in most cases of fungal endophthalmitis.

Ophthalmologist review for patients at risk of developing eye involvement during the course of a systemic infection is indicated. The diagnosis of endogenous endophthalmitis is typically confirmed following microbiologic evidence of infection in an intraocular specimen (aqueous or vitreous), and from blood samples (positive cultures) [148, 149]. Fungal growth can be confirmed by Giemsa stains. Polymerase chain reaction (PCR) primers and diagnostic vitrectomy can help in case of negative cultures [150]. For endogenous bacterial endophthalmitis, systemic antibiotics are supplemented with intravitreal antibiotics [137]. On the other hand, endogenous fungal endophthalmitis is treated with intravenous fluconazole, or voriconazole combined with systemic and intravitreal caspofungin. The need for vitrectomy (to obtain a sample of tissue for Giemsa, PCR for Candida, cultures) can be imperative and has to be accompanied with concomitant intravitreal injection of amphotericin B or voriconazole to avoid the development of adhesions [151].

CONCLUSION

Acute infective endophthalmitis remains a devastating complication following intraocular surgery and trauma. Although not entirely preventable, advances in surgical techniques and equipment along with new prophylactic measures have significantly reduced its incidence. Management of ocular surface disease prior to surgery, preoperative antisepsis with povidone–iodine, meticulous equipment sterilization and intracameral antibiotic use are essential to minimize the risk of infection.

Prompt diagnosis and accurate identification of the causative organism is important especially in cases that fail to respond to initial broad spectrum antibiotic treatment. Intravitreal antibiotic injections remain the mainstay of treatment and although Endophthalmitis Vitrectomy Study guidelines refer to post-cataract endophthalmitis they generally apply to all endophthalmitis categories. However, advances in vitreoretinal surgery may expand the role of vitrectomy in the management of acute infections attaining improved treatment outcomes.

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