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Endophthalmitis – a threat to the eye

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Resumo:

A Endoftalmite é uma doença potencialmente devastadora que envolve as estruturas internas do olho. É classificada em exógena, o subtipo mais comum, e em endógena, com base na origem da infeção. A endoftalmite exógena é causada por inoculação direta do olho por *microorganismos* do meio externo, e surge mais frequentemente como uma complicação de uma cirurgia oftalmológica, injeções intravítreas ou de trauma penetrante, enquanto a endoftalmite endogena é causada pela propagação hematogénica de *microorganismos* de outras localizações no organismo. Tem um diagnóstico clínico e quando suspeitada, amostras devem ser obtidas de forma a isolar o *microorganismo* causador em coloração gram, culturas e por polymerase chain reaction (PCR). O passo mais importante do tratamento é a administração direta intraocular de antibióticos. Antibióticos de largo espectro com cobertura de *microorganismos* gram-positivos e gram-negativos devem ser iniciados após a obtenção das amostras, e subsequentemente ajustados de acordo com o antibiograma. Apesar do tratamento adequado, o prognóstico a nível da acuidade visual é reservado e por isso medidas asséticas de prevenção são importantes. A iodopovidona é a única intervenção pré-operatória que permite a redução do risco da taxa de endoftalmites. No que diz respeito à cirurgia de catarata, a profilaxia com administração de 1mg de cefuroxime no final do procedimento parece ter benefício na redução da incidência de endoftalmites.

Palavras-chave: Endoftalmite; Acuidade visual; Técnicas de assepsia; Rara; Iodopovidona

Abstract:

Endophthalmitis is a potentially devastating condition involving the internal structures of the eye. It is classified based on the source of infection, as exogenous, the most common subtype, or endogenous. Exogenous endophthalmitis is caused by direct inoculation of the eye by *microorganisms* from the external environment, most frequently as a complication of ocular surgery, intravitreal injections or penetrating trauma, whereas endogenous endophthalmitis is caused by hematogenous spread of *microorganisms* from distant sites of the body. It has a clinical diagnosis and when suspected samples should be obtained for isolating the causative *microorganism* in gram staining, culture, and polymerase chain reaction (PCR) test. The most important step of treatment is the direct injection of antibiotics into the eye. Empiric gram-positive and gram-negative antibiotic coverage should be initiated, after obtaining cultures, and subsequentialy adjust to the antibiotic susceptibility. In spite of appropriate treatment, visual outcomes tend to be poor and preventing antiseptic measures are key. Povidone-iodine (PI) is the only preoperative technique with evidence of risk reduction in the rates of endophthalmitis. Regarding cataract surgery, the administration of 1mg of cefuroxime seems beneficial in reducing the incidence of endophthalmitis.

Keywords: Endophthalmitis; Visual acuity; Antiseptic techniques; Rare; Povidone-iodine

Índice

1. Introduction

Endophthalmitis is a rare, but severe and potentially sight-threatening disease presented with marked inflammation of intraocular tissues and fluids (vitreous and aqueous), usually due to infection.[1, 2] This clinical condition can be further classified as exogenous and endogenous endophthalmitis based on the transmission route of the infection.

Exogenous endophthalmitis is caused by direct inoculation of the eye by *microorganisms* from the external environment, most frequently as a complication of ocular surgery, intravitreal injections or penetrating trauma. [1] More over, it can also be caused by contiguous spread from adjacent tissues. Endogenous endophthalmitis is less common and is caused by hematogenous spread of *microorganisms* from distant sites of the body, through mycotic emboli.[3, 4]. This condition usually remains confined to the eye, but it can spread from the globe of the eye to the adjacent soft tissues of the orbit, called panophthalmitis. [5]

The incidence of endophthalmitis depends on the mode of inoculation. Recent reports suggest an estimated incidence between 1/2000 to 1/3333[6] following cataract surgery and 1/3000[7] in post-intravitreal injection (IVI). Regarding bleb-related endophtalmitis, the incidence can be up as 1.3%/patient/year for superior blebs and as 7.8%/patient/year for inferior blebs. [3, 8, 9] When considering clear corneal incision, silicone intraocular lens implants (IOLs) and surgical complications (e.g. rupture of the lens capsule) the incidence can be higher, since these are procedures that significantly increased the risk of endophthalmitis. In contrast, the use of intracameral cefuroxime significantly reduces this risk.[10]

Risk factors include advanced age, diabetes mellitus, blepharitis, poor patient cooperation during eye injection, use of antifibrotic agents, chronic bleb leak, a thin avascular bleb, bleb manipulation, bacterial conjunctivitis and accidental trauma.[7,11,12,13]

From a clinical point of view, most cases present itself acutely, developing symptoms within hours to a few days[5], including decreased visual acuity , irritation,

discharge, conjunctival injection and hyperemia, eye pain and eyelid edema. Since these are usually non-specific, early diagnosis is challenging and relies on the alertness of clinicians. This disease is considered a medical emergency, as delay in diagnosis and treatment may lead to permanent vision loss and potentially loss of the eye. [4, 5] Permanent sight loss in endophthalmitis may occur by a number of mechanisms, including exposure to bacterial toxins, vascular occlusion, retinal necrosis and detachment.[4]

When suspected, empiric gram-positive and gram-negative antibiotic coverage should be initiated, after obtaining samples. Isolating the causative organism for gram staining, culture, and polymerase chain reaction (PCR) test is the mainstay in guiding treatment.[3] However, even if cultures come back negative, the diagnose cannot be excluded and the patient should be treated accordingly.

2. Classification

2.1 Exogenous Endophthalmitis

Exogenous endophthalmitis is caused by direct inoculation of the eye by *microorganisms* from the external environment or by contiguous spread from adjacent tissues, usually following an intraocular surgery, intravitreal injections or a penetrating trauma. This condition is a detrimental complication following surgery and can be classified as acute or chronic based on the interval between the procedure and the onset of symptoms. It is considered acute if symptoms develop within less than 6 weeks after surgery, and chronic if it initiates after that period (≥6 weeks).[14]

According to the literature, sources of infection usually include bacterial colonization from the patient's eyelid margin or conjunctiva, healthcare personnel, surgical instruments, solutions or intraocular lens contamination. The incidence of exogenous endophthalmitis can range between 0.046% [15] after vitrectomy, up to 0.03% to 0.2% [3] after cataract surgery. When regarding post-traumatic endophthalmitis, the percentage can be as higher as 16,5%.[16]

2.1.1 Acute Postoperative Endophthalmitis

Acute postoperative endophthalmitis occurs within less than 6 weeks of an ocular procedure, like cataract surgery, or less frequently, penetrating keratoplasty[17], scleral buckling[18], glaucoma drainage device implantation/trabeculectomy, pars plana vitrectomy[19] and others.

Cataract surgery is one of the most common eye operations performed worldwide and is responsible for the majority of these cases.[20, 21] For the last 30 years the Endophthalmitis Vitrectomy Study (EVS), conducted in the 90s, has been the core base for management of postoperative endophthalmitis, as it is the only multicentre, prospective, randomized clinical trial to date. However, it only included data regarding cataract surgery. Since then, tremendous progress has been achieved in ocular surgery management, enhancing safer procedures and better outcomes.[22]

Sources of infection in postoperative endophthalmitis include bacteria colonized on the patient's eyelid margin or conjunctiva, or healthcare personnel, surgical instruments, solutions, and intraocular lens contamination.[14]

Ocular surface bacteria can contaminate the aqueous humor in operations, but endophthalmitis is rare. This may be because the aqueous humor has a rapid turnover time (100 min). However, the vitreous humor does not regenerate, so it's more susceptible to infection. [5]

The infectious process undergoes an initial incubation phase which may be clinically unapparent, lasting at least 16-18 hours, but **s**ymptoms most frequently occur within 1 week postoperation. Patients seem to present with decreased visual acuity, conjunctival injection, eye pain[23] and eyelid edema.[24, 25] Hypopyon may be present in 80% of cases[26], as well as white blood cells in the aqueous and vitreous humour, which can make the view of retina hazy, not allowing the identification of retinal vessels.[27] These signs

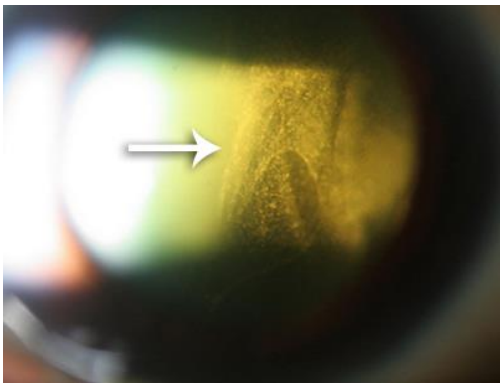

Fig. 1 Cells in the vitreous humor

Retina Vitreous Associates of Florida (2023). Fundoscopy – dilated retinal evaluation

and symptoms vary in degree depending on the underlying procedure. Patients usually present well despite local symptoms.

Risk factors associated to surgery may be divided into three domains: preoperative, perioperative and postoperative risks. Preoperative risk factors include blepharitis, ectropion, diabetes mellitus, older age (> 80), male sex, rural residence and immunosuppression. [19, 28]

When it comes to perioperative risks, the use of preoperative steroids are to be considered. Intraoperative complications, specifically posterior capsular rupture, seem to be related to the increased use of surgical instrumentation and prolonged operative time, which further increases exposure to the extraocular bacterial flora. Silicone and polymethyl methacrylate (PMMA), rather than acrylic intra-ocular lenses (IOLs) seem to also increase this risk. [27, 29]

In respect of postoperative risk, they include inpatient status, wound leak on postoperative day one and unsutureless clear corneal incisions with possible postoperative hypotony, which may allow ingress of *microorganisms* from the ocular surface. Some authors also advocate that late application of topical antibiotics, a day after surgery instead of the same day of operation, and the usage of older generations of fluoroquinolone antibiotics, may raise the risk of postoperative endophthalmitis.[19,30]

Gram-positive bacteria seem to be the more frequently isolated organisms among culture-positive cases. Among these, coagulase-negative staphylococci, specially *S. epidermidis*, are the most common. *Staphylococcus aureus* and Streptococci are also highly considered.[23] Less frequently other gram-positive cocci, including enterococci, and gram-negative bacilli are found.[5] Candida albicans was also recorded to be one of the most commonly isolated fungi.

2.1.2. Chronic Postoperative Endophthalmitis

Chronic postoperative endophthalmitis occurs within 6 or more weeks of an ocular procedure. Some of these include glaucoma filtering blebs, corneal sutures, fistulas from previous trauma and clear corneal wound leak. Chronic postoperative

endophthalmitis is less common than the acute postoperative endophthalmitis. In these cases, the *microorganisms* are usually sequestered in the capsular bag where it is more difficult for the immune system to reach.

This pathology usually has a slower progression, may involve only mild inflammation and can affect exclusively the anterior chamber. The most frequent symptom is decreased visual acuity and characteristic white plaques within the capsular bag are frequently seen in slit lamp examination.[5] It is less associated with hypopyon and pain, may or may not, be present.[3]

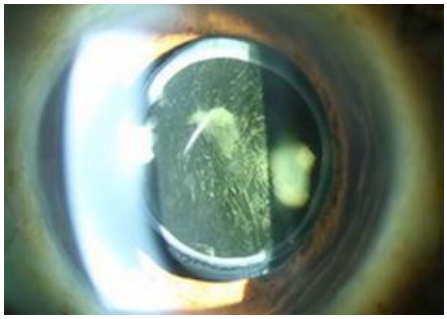

Fig. 2 White Plaques in the capsular bag

Titiyal, J.S., Agarwal, E., Angmo, D. et al. Comparative evaluation of outcomes of phacoemulsification in vitrectomized eyes: silicone oil versus air/gas group. Int Ophthalmol 37, 565–574 (2017). https://doi.org/10.1007/s10792-016-0305-5

When considering the risk factors, delayed-onset postoperative endophthalmitis may result from an acquired weakness in the ocular surface allowing late entry of organisms.[31] Chronic postoperative endophthalmitis seems to be associated with less virulent organisms, introduced at the time of intraocular procedure. *Propionibacterium acnes* is the most frequent causative organism isolated in culture-positive cases and fungal infections seem to also play an important role. [32]

2.1.3. Bleb-associated Endophthalmitis

A filtering bleb is a treatment for glaucoma. Bleb-associated endophthalmitis may occur in either an acute onset, within 4 weeks or, more commonly, in a chronic onset, within more than 4 weeks.[33]

It can have an insidious onset, and early symptoms may be mistaken for an ocular surface disease or conjunctivitis. Prodromal symptoms as headache, browache and conjunctivitis can be present. Early symptoms of infection usually include decreased vision, conjunctival hyperemia, discharge, irritation and pain. Typical findings include conjunctival injection, mucopurulent infiltrate at the bleb site, and sometimes bleb leaks. [19] A relative afferent pupillary defect can be present.[34] Critical evaluation of bleb morphology is key to early diagnosis of possible infection, including evaluation of bleb wall and any sign of milky-white mucopurulent infiltrates within the bleb and/or surrounding conjunctiva. In later stages, inflammatory cells, hypopyon, and vitritis can be present. [19]

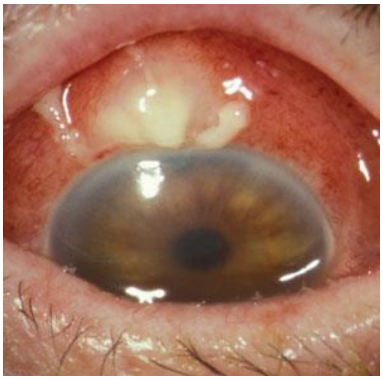

Fig. 3 Mucopurulent infiltrate

Mangan, R. In Review of Optometry. (2015). Knowing the signs of infection can help minimize the risk of blebitis progressing to Bleb-related endophthalmitis after glaucoma filtering surgery.

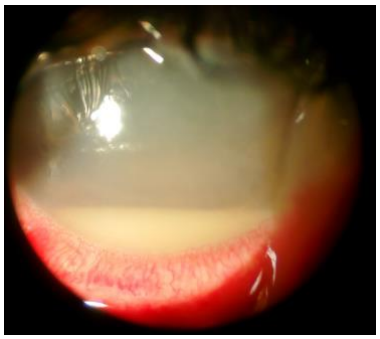

Fig. 4 Hypopyon

Xu, D. et al. (2021). Endophthalmitis. American Academy of Ophthalmology

The risk factors include a history of previous blebitis, late-onset bled leak, younger age, male gender, diabetes mellitus [19], use of antimetabolites during surgery or anti-fibrotic agents, inferior blebs (given the exposure to the tear lake containing bacterial organisms), thin avascular bleb, myopia, blepharitis and chronic antibiotic use.[11, 12, 13] Cystic and thin-walled blebs are more susceptible to infection than thick-walled blebs, as they have higher risk of leaks.[35]

However, the most important risk factor is tube or implant erosion, which significantly increases the endophthalmitis rate. It usually occurs within more than 2.5 years after surgery. Prophylactic antibiotic use has not prevented infections after trabeculectomy or GDI (glaucoma drainage implants). In fact, antibiotic use has lead to the increase prevalence of resistant *microorganisms*, making it difficult to treat endophthlamitis.[36]

Similar to acute postoperative endophthalmitis, coagulase-negative staphylococci, specifically *S. epidermidis*, and *S. aureus* are the most common organisms in acute bleb-associated endophthalmitis. Other common causative species include *Haemophilus influenzae* and *Pseudomonas aeruginosa*, although many other organisms have been reported.[37] In chronic bleb-associated endophthalmitis streptococcus species and gram-negative organisms, specifically *Moraxella catarrhalis*, are the predominant. [34]

2.1.4. Postintravitreal Injection Endophthalmitis

Endophthalmitis seem to be an important complication of intravitreal injections, specially following the injection of triamcinolone acetonide and anti-VEGF agents, such as bevacizumab, ranibizumab, pegaptanib and aflibercept. [5, 38]

Noninfectious endophthalmitis may also occur, specially after aflibercept, bevacizumab and triamcinolone acetonide injections. Although the etiology is poorly understood, it may represent an inflammatory reaction to a component in the medication vehicle or migration of triamcinolone acetonide crystals. [39]

Postintravitreal injection endophthalmitis typically occurs within the first few days after the injection, however it can occur several weeks later. Just like other types, the most frequent presenting signs and symptoms are decreased vision, eye pain and redness, with presence of anterior chamber cells, hypopyon and vitritis. Not all signs or symptoms are required for diagnosis. [40]

Risk factors include older age, diabetes mellitus, blepharitis, subconjuctival anesthesia, patient movement during the injection and the use of compounded medications. [41]

The most common isolated *microorganisms* are coagulase-negative Staphylococci and Streptococcus species, with focus on *Streptococcus viridans.* [42, 43] Less common organisms found are *Bacillus cereus*, *Enterococcus faecalis*, *S. epidermidis* and *S. aureus.* Endophthalmitis following intravitreal anti-VEGF agents caused by Streptococcus species has been reported to have the worst visual acuity outcomes.[31]

However, recent studies on this subject revealed that updated standard aseptic procedures, has helped to reduce the risk of infection related to intravitreal injections, to an incidence as low as 0,0074%.[44] However, there is no evidence supporting the benefit of antibiotic prophylaxis in preventing endophthalmitis after intravitreal injection. [45]

2.1.5 Post-traumatic Endophthalmitis

Post-traumatic endophthalmitis is an uncommon, but relevant complication of open-globe injury, having a higher incidence when an intraocular foreign body is present. [46]

The onset of symptoms depends on the mechanism of injury and the virulence of the organisms involved. It is normally established between 12 to 24 hours after the trauma.[5] Diagnosis can occur within hours or years after the initial injury.[47] It clinically presents with hypopyon, decreased vision, red eye, pain out of proportion to the degree of trauma, retinitis, vitritis, retinal necrosis, periphlebitis, corneal and/or lid edema and loss of red reflex. Findings include marked intra-ocular inflammation and often a ring corneal infiltrate. [5]

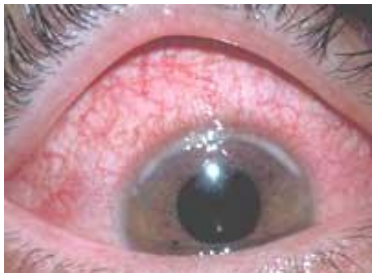

Fig. 5 Ring corneal infiltrate

Ocular Surgery News. (2007). Patients with corneal infiltrates.

Risk factors include retained intraocular foreign body, traumatic lens rupture, corneal wound, retinal break or detachment, traumatic cataract or posterior lens rupture, dirty wound, long hospital stay, rural location, delayed wound closure, delayed prophylactic systemic antibiotics and delayed primary repair >24h. Metal rather than glass or blunt trauma injuries are also risk factors. Tissue prolapse (iris, vitreous) and presence of hyphema may reduce the risk of endophthalmitis as it may act as a barrier against entrance of organisms. [5, 48, 49]

The causative *microorganisms* are either from the normal flora surrounding the eyelid area, gaining entry after a delay in primary wound closure, or are carried into the wound by contaminated injury-causing objects. [14]

The majority of these cases are caused by bacteria, being the more frequent gram-positive cocci, such as *S. epidermidis*, *S. saprophyticus* and streptococcus species. Gram-positive bacilli, such as *Bacillus cereus* is a major pathogen, which may cause a fulminant infection.[50] Within fungal posttraumatic Endophthalmitis Aspergillus species are the most prevalent.[48, 51]

2.2 Endogenous Endophthalmitis

Endogenous endophthalmitis is caused by inoculation of the eye by infectious pathogens spread systemically through the bloodstream and across the blood-ocular barrier. It is not frequent and accounts for a small part of all reported Endophthalmitis cases. [52] Panophthalmitis, a severe form of endophthalmitis, can involve tissue adjacent to the orbit, but the infected eye alone does not ever serve as the source of bacteremia or fungemia. [14]

Symptoms vary depending on the severity and extent of infection. They include decreased vision, eye pain, photophobia, floaters and eyelid swelling. [14] Ocular signs include hypopyon, subconjunctival haemorrhage, conjunctival injection, iritis/retinitis, corneal edema, anterior chamber cells and reduced or absent red reflex. As it occurs as a secondary complication of a systemic infection, systemic findings may also be present. [53]

Although it is caused by hematogenous spread, endogenous endophthalmitis tends to develop unilaterally, with the right eye more commonly affected, possibly due to the more proximal and direct arterial route from the heart to the right carotid artery.[14] Bilateral disease occurs in a minority of cases. [54]

According to many recent studies, it affects mostly patients aged between 30 to 40 years old, being more common among patients with hepatitis C infection. Other less common comorbidities include HIV infection, with or without AIDS, syphilis, intravenous drug use, indwelling catheter, endocarditis, septic arthritis, meningitis, diabetes mellitus, end-stage renal or liver disease, malignancies and imunosupression.[5,54,55] According to a worldwide systematic survey of endogenous bacterial endophthalmitis,

diabetes was the most common predisposing medical condition, and liver abscess was the most common extraocular focus of infection.[56]

The *microorganisms* involved in this kind of infection appear to be affected by the geographic location and origin of the extraocular loci of infection. However, fungi were the most commonly isolated *microorganisms* in several series of endogenous endophthalmitis, being the leading one the *Candida Albicans*, specially in intravenous drug users [57, 58] and central lines, followed by Aspergillus species.[59] When caused by bacteria it is typically due to *S. aureus*, from cutaneous infections, streptococci spp, in endocarditis, and gram-negative species, such as *E. coli*, when associated with urinary tract infection, diabetics and liver abcess.[60,61] Fungal and gram-negative endophthalmitis are generally associated with poorer visual outcomes than endophthalmitis secondary to gram-positive organisms. [4]

3. Diagnosis and Differential Diagnosis

Endophthalmitis is a clinical diagnosis, initially suspected based upon clinical presentation, and subsequently confirmed with laboratory testing of vitreous or aqueous humor. Isolating the causative organism for gram staining, culture, and polymerase chain reaction (PCR) test is the mainstay in guiding treatment. However, when suspected, empiric broad-spectrum antibiotics should be initiated and subsequentialy adjust to the antibiotic susceptibility. [3]

Vitreous specimens provide more accurate and reliable culture results than do aqueous cultures.[62, 63] Samples should be obtained at presentation, as early as possible, and sent for bacterial and fungal cultures, although a negative culture occurs in 30% of cases. [5] Although each individual culture source may not have high enough sensitivity to capture the infectious organism, the combined results of multiple culture sources yield the best chance of detecting the pathogen.

When it comes to endogenous endophthalmitis, the diagnosis can sometimes be aided by the presence of systemic signs and symptoms of infection and also by blood cultures. However, endogenous endophthalmitis may occur in patients with no signs of systemic infection.[64] As many cases of endogenous endophthalmitis may be culture negative, targeted PCR for suspected bacteria or fungi may be helpful.[65] Moreover, positive rates of vitreous and aqueous specimens detection are generally higher than those of blood cultures. [66]

In patients who have known candidaemia and eye findings compatible with chorioretinitis, vitreous culture is usually not necessary.[5] B-scan ultrasonography is recommended especially in culture-negative cases.[67] Even if cultures come back negative, the diagnose should not be excluded and, in case of doubt, the patient should be treated accordingly.

The diagnosis of posttraumatic endopthalmitis may be challenging as the signs and symptoms of endophthalmitis may overlap with those of the initial injury. As such, the presence of hypopyon, vitritis, and/or worsening pain should be considered possible signs of infection.[68] Another important diagnostic step in posttraumatic endophthalmitis is the use of imaging techniques to identify the presence of occult IOFBs. In one series, IOFB was identified by clinical examination in 46% of cases, by B-scan echography in 52%, and by computed tomography (CT) in 95%.[69] Magnetic resonance imaging (MRI) may be considered after CT scan (so that metallic IOFBs are ruled out) to better identify non-metallic IOFBs.

The multitude of diagnostic imaging techniques available for detection of IOFBs affords varying levels of specificity for foreign bodies of various compositions. Plain X-rays, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) may be considered, however it is generally accepted that CT, especially helical is the most reliable method, regardless of the location of IOFB and is recommended as the first- line diagnostic modality.[69, 72]

Vitreous specimens have been traditionally obtained by vitreous tap using a needle and syringe. Other options include using vitrectomy cutters and office-based automated vitrectors. No difference has been shown in the positivity of cultures

obtained from vitreous tap versus vitrectomy.[63] When considering fungal infection, victrectomy seems to be the most accurate sample obtaining method for culture.[70] An aqueous sample should be obtained, through a needle aspirate in the anterior chamber, including aspiration of hypopyon material when present.[19] Conjunctival cultures poorly correlate with culture results obtained from anterior chamber or vitreous and should not be used for tailoring of antibiotic use.[35, 37]

In needle aspiration, usually an A22 to 27G needle attached to a syringe is inserted into the vitreous cavity through the pars plana (pull plunger back first to break the vacuum before inserting into de eye). Slowly aspirate. If no fluid vitreous can be obtained with a needle tap, an anterior chamber tap or vitreous biopsy must be performed instead to avoid aspirating formed vitreous.[2]

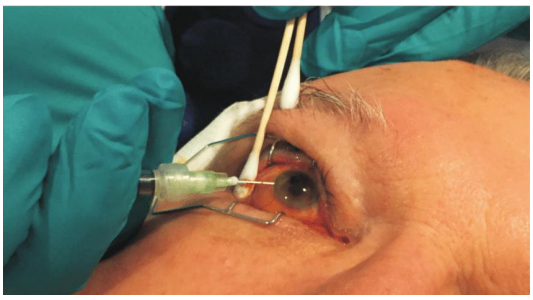

Fig. 6 Anterior chamber needle aspirate

Bach, A., Filipowicz, A., Gold, A.S., Latin, A., Murray, T.G. (2017). Paracentesis following intravitreal drug injections in maintaining physiologic ocular perfusion pressure

A vitrectomy is performed in the operating room with a vitrector, which cuts and aspirates the vitreous humor usually without saline solution replacement. The result is 1cc of vitreous humor, which may be vacuum-filtered through a 0.45um filter. The filter paper can then be cultured.[5]

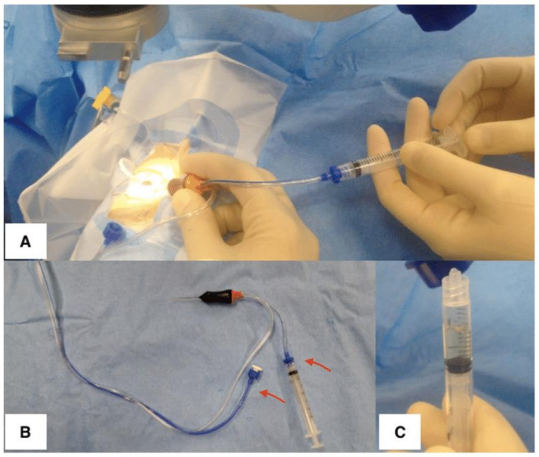

Fig. 7 Vitrectomy for vitreous humor sample

Mastropasqua, R., Carlo, E.D., Sorrentino, C., Mariotti, C., Cruz, L. (2019). Intraocular Biopsy and ImmunoMolecular Pathology for "Unmasking" Intraocular Inflammatory Diseases

The other option is to perform the procedure as soon as possible, perhaps in an eye casualty or procedure room setting. While this may be more prompt, it has the disadvantage of a less sterile environment, with higher concern for contaminating organisms.[71] If office-based management with intravitreal injections is performed, then ongoing evaluation should be performed to reassess the need for vitrectomy in cases of worsening vitritis or absence of improvement.[54]

Vitreous tap has the advantage that it requires largely the same anesthetic and operative set-up as the intravitreal antibiotic injection, which is commonly performed immediately afterwards as treatment.

The question of when to perform tap and inject versus surgical intervention with vitrectomy has been well established in the EVS (Endophthalmitis Vitrectomy Study) regarding only post-cataract endophthalmitis patients. The study found immediate vitrectomy was only beneficial for patients who presented with light perception vision. For others, both procedures were equivalent.[19]

When regarding positivity of samples, gram stains are positive in about 40–50% of cases. When talking about specimens cultures, this percentage can be much higher. Vitreous cultures are more likely to be positive after vitrectomy, reaching up to 90%, than vitreous aspirate, in about 75% o cases. Regarding aqueous humor, cultures are positive in about 40% of cases.[32]

Polymerase chain reaction (PCR) has a lower false-positive rate when it comes to excluding commensal organisms. The major advantage of this tecnique is rapid access to results, with some microbial detection happening between 30-50 minutes, as compared to 1-14 days for previous methods. Another advantage of PCR is its ability to test for wide ranges of organisms in only one process, not requering the organisms to be alive at the time of testing.[71] Sensitivities of PCR and culture were similar with initial intra-ocular samples, before antibiotics had been injected.[73] In one study, cultures were positive in 75% and PCR was positive in 91%.[74] However, PCR was much more sensitive than culture (70% vs. 9%) in subsequent vitrectomy samples, possibly due to either the inhibitory effect of the previously injected antibiotics or the fact that PCR does not distinguish living from dead *microorganisms*. A study also found improved sensitivity with PCR, in which 19 patients with endophthalmitis, 18 were positive by PCR and only ten by culture.[75] In chronic postoperative endophthalmitis, intraocular cultures may be negative, although, when present, culture of the white capsular plaque, is often positive.[5]

Additionally, it'is important to consider potential mimickers of endophthalmitis, including noninfectious inflammation. Somo examples are toxic anterior segment syndrome, retained lens material, vitreous hemorrhage, flare-ups of previous uveitis and others.[3] Toxic anterior segment syndrome (TASS) is a sterile postoperative inflammatory reaction caused by a non-infectious substance that enters the anterior segment and results in toxic damage to intraocular tissues. [129] It mimics endophthalmitis due to its clinical similarities. In order to diferentiate them, one should reminde that the most important feature of differentiation between the two is that TASS is usually associated with fibrin formation in the anterior chamber without the involvement of the vitreous as is in the case with infectious endophthalmitis. Other distinguishing features of TASS include early onset (12-24h postoperatively), limbus-to-limbus corneal edema, iris damage (fixed, dilated or irregular pupil, iris transillumination defects), high intraocular pressure and the fact that it usually improves with corticosteroid treatment. [129] All these conditions are associated with obvious inflammatory reactions and hypopyon may clinically mimic infectious endophthalmitis.[76]

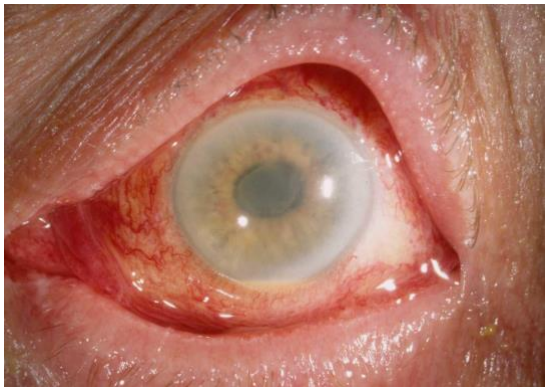

Fig. 8 Toxic Anterior Segment Syndrome

Deschênes, J. *In Medscape* (2023). Toxic Anterior Segment Syndrome (TASS)

Diagnosis of endophthalmitis depends mostly on the clinical findings of ophthalmological examination. In the absence of ocular trauma or surgery, systemic investigations should be performed immediately to look for possible sources of infection or presence of malignancy such as retinoblastoma in children, leukemia, or intraocular lymphoma, which may act like a panuveitis.[3]

Since ocular and systemic symptoms of endophthalmitis are typically non-specific, early diagnosis relies on the alertness of ophthalmologists and other physicians. Physicians should be advised to assess the eyes of septic patients, especially in those who are unconscious and should be aware that major systemic infections can manifest initially in the eye.

Further advances in the microbiology diagnosis including polymerase chain reaction (PCR) and newer molecular application of peptide nucleic acid–fluorescence in situ hybridization (PNA-FISH) are promising diagnostic tools but their clinical usefulness remains uncertain.[77]

Moreover, when regarding diagnosis in the era of novel microbial detection techniques, Matrix-Assisted Laser Desorption Ionization–Time of Flight (MALDI-TOF) Mass Spectrometry[78] and the use of magneto-DNA nanoparticle system are becoming emergent techniques, the latter had been able to simultaneously identify 13 species of bacteria in under 2 hours, thus enhancing diagnosis. [79] These seem promising and could potentially be used in rapid diagnosis of endophthalmitis causes in the near future.

4. Treatment

When endophthalmitis is suspected, empiric gram-positive and gram-negative antibiotic coverage should be initiated, after obtaining cultures. Even if cultures come negative, the diagnose cannot be excluded and the patient should be treated accordingly.

The most important component of treatment is the direct injection of antibiotics into the eye, usually performed after a sample is obtained. Initially, broad-spectrum antibiotics are used empirically. A combination of Vancomycin (1mg/0.1mL) plus Ceftazidime (2.25mg/0.1mL) is injected intravitreally as first-line treatment, and Vancomycin plus Amikacin (0.4 mg/0.1mL) is used as a second-line. [80] Each agent is diluted in 0.1mL of sterile water or saline. The combination of vancomycin with ceftazidime form a white precipitate when mixed and for this reason many surgeons choose to deliver these drugs in separate syringes using separate needles. [81] The choice for these antibiotics are due to a near 100% coverage of gram-positive species by vancomycin, and an excellent coverage for gram-negative bacteria by ceftazidime.[82] Also, Ceftazidime is preferred over amikacin because of the small risk of macular infarction with injected aminoglycosides.[83] Benzylpenicillin (0.18mg/0.1ml) can be

considered instead of ceftazidime if confirmed or presumed Streptococcus spp. infection. [81]

Antibiotic concentrations in the vitreous decline rapidly and most last only 24 to 48 hours. Thus, one injection of antibiotics may not maintain levels in the vitreous long enough to kill all bacteria and repeat injection of vancomycin or ceftazidime may be indicated after 48 hours if there is persistent or worsening intraocular inflammation. The second injection of amikacin is usually avoided given the retinal toxicity concerns[5] but choice of antibiotic for repeat intravitreal injection is based on the culture result. [84]

In more severe cases with massive bacterial postoperative endophthalmitis infection a simultaneous intravitreal injection of unpreserved dexamethasone and broad-spectrum antibiotics combination is indicated.[85] More recent studies have demonstrated no adverse effects of intravitreal dexamethasone, with faster resolution implied and less need for repeat intravitreal antibiotics.[86] The potential inadequate coverage of first-line antibiotics should caution the surgeon in using intravitreal steroids until the pathogen and its drug sensitivities are known. In cases where fungal endophthalmitis is suspected, intravitreal steroids are routinely avoided due to concerns regarding fulminant infection.[87] In cases of fulminant refractory acute postoperative endophthalmitis with rapidly worsening visual acuity, complete vitrectomy operation is the fundamental option to debride ocular pus.[88]

Vitrectomy surgically debrides the vitreous humor, similarly to draining an abscess, and is the fastest way of clearing infection in eyes with fulminant endophthalmitis. In post-cataract endophthalmitis with severe vision loss or rapidly worsening vision vitrectomy should also be performed, as in EVS study was shown that it decreased the rate of severe vision loss from 47% (tap group) to 20% (vitrectomy group), prior to intravitreal injection of antibiotics.[5]

In chronic endophthalmitis, total capsulectomy and removal of IOL may be considered for recurrent cases. Treatment with a combination of removal or exchange of the IOL, total capsulectomy, vitrectomy and intravitreal antibiotics has been the most successful approach with treatment regimens that leave the original IOL in place having a 40–50% relapse rate. [5]

The role of systemic antibiotics in the treatment of exogenous endophthalmitis remains controversial. Whether these provide any additional benefit to intravitreal antibiotics is unknown. The EVS study reported that systemic amikacin and ceftazidime had no effect on the final visual outcome.[31] These antibiotics have poor activity against staphylococci, a major organism in acute postoperative endophtalmitis, and these antibiotics fail to cross the blood ocular barrier, reaching minimal levels in the vitreous humor.[3]

On the other hand, systemic ciprofloxacin and moxifloxacin had reported a faster resolution of hypopyon and a decreased need for repeat intravitreal antibiotics in patients with acute postoperative endophthalmitis because these drugs cross the blood ocular barrier.[89] This also seems to be true for bleb-related endophthalmitis due to its association with high virulence organisms. Additionally, experimental studies have documented the safety and efficacy of intravitreal fluoroquinolones, including levofloxacin and moxifloxacin, against causative intraocular organisms.[80, 81]

To date, there are no randomized clinical trials regarding the treatment of postinjection endophthalmitis. Since the most common isolates in both acute postoperative and postinjection endophthalmitis are Staphylococcus species, many clinicians use the EVS as a guideline for endophthalmitis following intravitreal injections.[3]

Similar to bleb-associated endophthalmitis, causative organisms in posttraumatic endophthalmitis are generally more virulent. It is generally agreed that primary closure of an open-globe injury is important and, if present, IOFB should be removed.[90] Treatment should be aggressive with vitrectomy.[5] In addition, a combination of intravitreal, subconjuctival, topical, and systemic antibiotics are also recommended, once the wound is closed.[16] A combination of topical vancomycin (50mg/ml) every hour, ceftazidime (50-100mg/ml) every hour and topical cycloplegics with or without associated steroids are administered at the onset of treatment.[16] For treatment of post-traumatic fungal endophthalmitis, it's recommend using intravitreal and systemic voriconazole as it covers the most common fungal *microorganisms*.[16]

Regarding endogenous endophthalmitis, treatment of the underlying source of bacteraemia with systemic broad-spectrum antibiotics is necessary, but this will not effectively treat the endophthalmitis. Intravitreal antibiotics and, usually, a vitrectomy are necessary. [5] Treatment should be started empirically without waiting for laboratory confirmation.[14] Systemic antibiotics and antifungals, amphotericin B, fluconazole or voriconazole, depending on the causative organism are generally recommended as endogenous endophthalmitis generally has extraocular loci of infection, specially when confirmed active bloodstream infection.[54] Although intravitreal amphotericin B and voriconazole appear similar in efficacy of treatment of fungal endophthalmitis, voriconazole may be preferable as amphotericin B has been associated with retinal toxicity in animal models.[91] The use of steroids is controversial due to inconclusive results in the literature.[92] Topical cycloplegics, steroids, or hypotensive agents can be used as adjunctive therapy to ameliorate inflammation and pain as well as secondary glaucoma.[14] Systemic antibiotics and antifungals may be transitioned from intravenous to oral administration once *microorganism*'s sensitivities have been determined.[54]

5. Prognosis

Presenting vision is the strongest predictor of visual prognosis[93] and the visual outcome is highly correlated with the bacteriology. Streptococci of any type produce severe endophthalmitis with a poor chance of visual recovery, whereas coagulase-negative staphylococci cause milder endophthalmitis in general.[5] The virulence factors, the infectious dose of inoculated pathogens, and their antibiotic sensitivity play a major role in the endophthalmitis' prognosis.[88] Other factors correlated to poorer outcomes include rapid onset, poorer presenting vision, a causative organism other than coagulase-negative Staphylococci, corneal edema, a hypopyon larger than 1.5mm, extensive media haze, absence of fundus visibility, and the presence of retinal detachments or intraocular foreign bodies. [93, 94] However, depending on the cause of endophtalmitis, prognosis may vary.

Despite the great advances in the management of postoperative endophthalmitis, the prognosis is not usually favorable due to associated poor visual outcomes, as only about 50% of the patients are able to achieve a final visual acuity of 20/40 or better. Furthermore, according to the EVS, 15% of patients had a final visual acuity of 20/200 or worse but in a more recent single-center series, this percentage was as high as 36%.[95]

The EVS reported that in patients with visual acuity of light perception (LP), when compared to tap and inject, prompt PPV was associated with a 3-fold increase in the proportion of patients achieving visual acuity of 20/40 or better, a 2-fold increase in the proportion of patients achieving visual acuity of 20/100 or better, and a decrease in the proportion of patients achieving visual acuity of worse than 5/200. In patients with better than LP initial visual acuity, however, tap and inject had comparable outcomes as PPV.[23] Based on these results, PPV is generally recommended in patients presenting with LP, and tap and inject is generally recommended for eyes presenting with visual acuity of better than LP. [3]

On the other hand, the prognosis is also compromised by the increased incidence of bacterial drug-resistance even with the growing era of optimal disinfectants and antibiotic delivery strategies.[96] Delayed-onset endophthalmitis has been reported to have generally more favorable final visual outcomes when compared to acute-onset cases. [97] In chronic postoperative cases, reported cases of eyes infected with P. acnes generally had a better final visual outcome while fungal cases were associated with significantly worse outcomes where more than one-fifth of these cases resulted in final visual acuity of worse than 20/200. [98]

For endophthalmitis occurring after cataract surgery, management with intravitreal antimicrobial injections has greatly contributed to achieving better outcomes (anatomic and functional). [31] In glaucoma, the visual outcomes are generally poor due to the preexisting reduced vision from glaucoma itself and the involvement of more virulent organisms. [99][100] Bleb-associated endophthalmits is also associated with unfavorable final visual outcomes due to high prevalence of virulent pathogens such as Streptococcus species and Gram-negative bacteria.[33]

Endophthalmitis cases following intravitreal injections have a high prevalence of more virulent Streptococcus species, approximately 3 times more prevalent than in postoperative cases, resulting in relatively poorer visual outcomes. [101] Visual outcomes have varied among studies with the proportion of eyes returning to preinjection visual acuity in three recent studies ranging from 33% to 78%.[102, 103] In another study, when compared to post-operative endophthalmitis, postinjection endophthalmitis was 6 times more likely to have worse final visual acuity and was much less likely to have improvement in visual acuity following treatment.[101]

Posttraumatic endophthalmitis is also associated with generally poor outcomes. Recent studies have reported that a final visual acuity of 20/40 or better was achieved in only 15%–40% of cases. [48] One series reported that a good final visual outcome, defined as 20/45 or better, was significantly associated with initial visual acuity of at least light perception and an absence of a pupillary fibrin membrane. [104]

When it comes to prognostic factors for open globe injurys with a retained intraocular foreign body (IOFB), studies demonstrate that many variables can be responsible for the final visual acuity. Increased IOFB mass was associated with posterior segment injury, retinal impact, visual acuity of ≤ 20/200, increasing complications and retinal detachment.[105] It's also shown that the size of the IOFB can play a role in postoperative visual acuity.[106] Due to its higher kinetic energy, a larger IOFB is more likely to cause serious damage and have a poor prognosis. Furthermore, the location and mechanism of injury are important factors. Injury limited to the anterior segment was found to be predictive of better final visual acuity than injury to the posterior segment. [107] Favorable visual outcomes were seen in eyes in which the IOFB did not damage the lens. In one study, there was no statistically significant association between corneal perforation and poor visual outcome. [105] However, wound length did contribute to worse visual outcomes. [107] However, no increase in rates of endophthalmitis or poorer visual outcomes was seen in patients where IOFB removal was delayed up to 36 hours.[108]

Among an endogenous endophthalmitis case series between 2001 and 2012 with a total of 89 eyes, a meta-analysis reported that 41% had a final visual acuity of at least 20/200 and 19% underwent enucleation or evisceration. These visual outcomes were

improved compared to cases treated prior to 2001, in which final visual acuity of at least 20/200 was seen in only 31%.[56] Among the pathogens typically found in endogenous endophthalmitis, cases caused by Aspergillus species are associated with the worst final visual outcomes and those caused by Candidia species with the best. In another series, while 80% of cases caused by Candidia had a final visual acuity of at least 20/200, only 18% of cases with Gram-positive bacteria achieved that visual acuity.[66]

The prognosis of injection drug use-associated endogenous endophthalmitis even with treatment is typically poor. However, there is great variation in outcomes, which may be attributed to low sample sizes, diversity of patient characteristics, delays in diagnosis, and differences in threshold for surgical treatment. In endogenous endophthalmitis, regardless of cause, bacterial infection appears to portend a worse prognosis compared with fungal infection with exception of Aspergillus in injection drug use cases.[66] Ocular sequelae contributing to diminished vision include cataract formation, vitreous hemorrhage, cystoid macular edema, epiretinal membrane, retinal tear, retinal detachment with or without proliferative vitreoretinopathy, and macular scarring. [54]

As expected, endophthalmitis caused by antibiotic-resistant *microorganisms* generally have poorer visual outcomes.[109]

6. Prophylaxis

Endophthalmitis can not be completely prevented, but its incidence may be reduced. It is globally accepted that the use of various antiseptic measures significantly reduces the rate of bacterial endophthalmitis. [110]

Numerous perioperative procedures have been attempted to avoid endophtalmitis as a complication. Measures taken to reduce the risk of postoperative endophthalmitis include management of ocular surface disease before surgery, including blepharitis which is associated with increased ocular surface microbial load,

the application of povidone-iodine to the cornea, conjunctival sac and periocular surface for 3 minutes before surgery, the use of face masks and meticulous sterilisation of instruments.[4]

Aqueous chlorhexidine application may be an acceptable alternative to decrease the risk of postinjection endophthalmitis. Topical chlorhexidine achieves similar antisepsis and may have lower discomfort rates compared with PI.[112] A recent study of over 40 000 intravitreal injections that only used aqueous chlorhexidine 0.05% or 0.1% for prophylaxis reported a low rate of endophthalmitis (approximately 1 in 13 500 injections), excellent patient tolerability, and only one case of suspected allergic reaction.[113]

Whilst copious irrigation by topical antiseptic povidone-iodine and chlorhexidine in the periocular area are considered to be the cornerstone in postoperative endophthalmitis preclusion, the possible corneal toxicity by chlorhexidine restricts its application in most settings.[110] However, the application of povidone-iodine (PI) to reduce the risk of postinjection endophthalmitis remains cost-effective. A single bottle of PI may be safely used to prepare injections in many patients, bringing the cost of prophylaxis to less than a few cents per patient.[111]

Moreover, multiple concerns have been raised about the use of prophylactic antibiotics, since they increase costs and may contributes to increasing bacterial drug resistance. The later being an important clinical challenge, as demonstrated by increasing resistance of the coagulase negative staphylococcus to flouroquinolones and cephalosporins, [114] and increased resistance to the antibiotics commonly used during cataract surgery.[115] The prophylactic role of topical antibiotics in postoperative endophthalmitis is unclear. Studies have shown that preoperative topical antibiotics significantly reduce conjuctival flora but it is unclear whether this actually decreases the rate of postoperative endophthalmitis. [116]

The use of preoperative and perioperative antibiotics varies within and between countries and regions of the world. The Centers for Disease Control and Prevention estimate that >50% of antibiotic use is unnecessary or inappropriate in the United States, with multiple guidelines discouraging the use of routine antibiotics. The

controversy regards the balance in exposing patients to the low risk of intraocular toxicity in an attempt to prevent another rare complication, endophthalmitis. [117]

However, a group of Swedish surgeons started the practice of administering a direct intracameral injection of cefuroxime at the close of cataract surgery to reduce endophthalmitis rates. Based on this practice, in 2007 the ESCRS (European Society of Cataract and Refractive Surgeons) conducted a prospective and randomized study across nine European countries regarding cataract surgery, designed to primarily answer if perioperative antibiotics prevent endophthalmitis and secondly, if so, how should they be administered, intracameral or topical. [129]

This study concluded that the risk for contracting postoperative endophthalmitis was significantly reduced, approximately 5-fold, by an intracameral injection of 1mg cefuroxime (in 0.1ml Normal Saline) at the close of surgery. The lowest incidence rate was observed where both cefuroxime and peri-operative topical levofloxacin were used. Aside from the countries included in the ESCRS study, other recent addition to the literature, originating worldwide, continue to support these findings of the ESCRS study. [129]

In addition, the use of topical drops preoperatively and/or postoperatively had no proven benefit over chlorhexidine 0.05% (PVI at one site only) preoperatively and with intracameral cefuroxime injected at the close of surgery. [129]

Regarding bleb-associated endophthalmitis there is little or no evidence that prophylactic topical antibiotics prevent it. On the contrary, it was reported that intermittent use or chronic use of antibiotics was associated with an increased risk of bleb-associated endophthalmitis.[11] Risk reduction of bleb-associated endophthalmitis should include addressing its risk factors such as early treatment of blebitis[118] and repair of leaking blebs. Irrigating the operative field again with 1.25% povidone–iodine after lid speculum placement and performing sclerotomy with some povidone–iodine remaining in the conjunctival sac may be helpful to prevent bacterial contamination of the vitreous. [119]

Post-injection and postoperative endophthalmitis is prevented by ensuring sterile conditions and techniques as mentioned before, with little evidence in the

literature to support the use of prophylactic antibiotics. [120] One study showed that the use of topical 5% povidone iodine was statistically significant in reducing the incidence of gram-positive endophthalmitis when compared to silver protein solution.[121]

The use of lid speculums has been traditionally recommended as part of a sterile protocol for administrating intravitreal injections. [122] However, one series reported that not using lid speculums did not increase the rate of postinjection endophthalmitis. Numerous studies have reported that prophylactic antibiotics do not reduce the incidence of postintravitreal injection endophthalmitis. [40] It has been reported that the use of topical antibiotics immediately after or for 5 days after injections were actually associated with higher rates of postinjection endophthalmitis, perhaps by altering conjunctival flora. [123] It has been suggested that prophylactic antibiotics are not a necessary part of intravitreal injection preparation and management.

Once again, antibiotic prophylaxis in posttraumatic endophthalmitis is controversial because there is very few randomized clinical trials evaluating their effects. Systemic antibiotics have been widely utilized in open-globe injuries[124] and the non-use of systemic antibiotics appears to be a risk factor for post-traumatic endophthalmitis.[125] In a prospective, randomized study assessing the prophylactic effects of intracameral and intravitreal antibiotics in posttraumatic endophthalmitis, there was a statistically significant reduction in rates of endophthalmitis in antibiotic-treated eyes with IOFB.[126] Evidence demonstrating a benefit of using prophylactic intravitreal antibiotics for ocular globe injuries without an IOFB is scarce and more research is needed in this area. However, Essex et al recommend consideration of prophylactic intravitreal antibiotics if at least two of the following three risk factors are present: delay in primary repair of ≥ 24 hours, dirty wound, or lens breach.[48] The decision to use prophylactic antibiotics in the absence of signs or symptoms of endophthalmitis is also still controversial.[90]

As the EVS was published, tremendous progress has been introduced in vitrectomy technology, which now permits the vitreoretinal surgeon to perform surgery more safely and with better outcomes. The burden of surgery on the patient is also dramatically reduced. Smaller incision vitreoretinal surgery with 25 and 27-gauge instrumentation is supposed to reduce the risk of PE as it prevents bacterial migration

into the eye during the procedure. In addition to switching to a complete, as opposed to a partial, vitreous removal, along with the moving up of the surgical intervention to as early as possible allows the prevention of complications that would limit the functional improvement postoperatively. [127]

Lastly, the only category evidence of risk reduction in the rates of endophthalmitis is the use of antiseptics techniques. Literature supports that povidone-iodine (PI) is the most effective form of preoperative antisepsis to reduce the risk of postoperative infection, not only for ophthalmology, but for all other surgical specialties. Bacteria do not develop resistance to PI, and PI is also effective against fungi and viruses.[110, 128]

Regarding cataract surgery, the literature is clear on the beneficial use of 1mg of cefuroxime at the close of surgery to reduce the incidence of Endophthalmitis. [129]

7. Conclusion

Endophthalmitis although rare, it is a medical emergency. As its diagnosis is clinical, physicians should be aware of its typical presentation and its possible first manifestation of a systemic underlying condition.

When suspected, samples should be obtained for isolating the causative *microorganism* in gram staining, culture and polymerase chain reaction (PCR) test, and empiric broad-spectrum antibiotics should be initiated.

The most important step in treatment is intravitreal injection of antibiotics and vitrectomy should be performed in case it fails. Systemic antibiotics are usually needed to treat the underlying infection in endogenous endophthalmitis.

Regardless of it's underlying cause the visual outcomes are usually poor so it is important to invest in its prevention. Although endophthalmitis cannot be completely prevented, its incidence may be reduced with the use of various antiseptic measures such as povidone-iodine (PI) that is the preoperative technique with evidence of risk reduction in the rates of endophthalmitis. Regarding cataract surgery, the

administration of 1mg of cefuroxime seems beneficial in reducing the incidence of endophthalmitis.

However, a lot of clinical trial data is yet to be collected and more studies regarding this disease are yet to be conducted as better and safer guidelines regarding all presentations of this disease are yet to be caracterized and well managed.

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Resumo:

A Endoftalmite é uma doença potencialmente devastadora que envolve as estruturas internas do olho. É classificada em exógena, o subtipo mais comum, e em endógena, com base na origem da infeção. A endoftalmite exógena é causada por inoculação direta do olho por *microorganismos* do meio externo, e surge mais frequentemente como uma complicação de uma cirurgia oftalmológica, injeções intravítreas ou de trauma penetrante, enquanto a endoftalmite endogena é causada pela propagação hematogénica de *microorganismos* de outras localizações no organismo.

Dentro da endoftalmite enxógena, inclui-se a endoftalmite aguda pós-operatória que compreende as endoftalmites que ocorrem em menos de 6 semanas após um procedimento oftálmico, a endoftalmite crónica pós-operatória que inclui aquelas que ocorrem 6 semanas ou mais após um procedimento oftálmico. Dentro deste grupo, inclui-se ainda as endoftalmites pós-trabeculectomia, pós-injeção vítrea e as pós-traumáticas.

Dentro da endoftalmite aguda pós-operatória, os sintomas são variáveis mas geralmente surgem dentro de 1 semana após o procedimento e incluem diminuição da acuidade visual, hiperémia, dor ocular e edema palpebral. À observação, a presença de hipópion é frequente, assim como a presença de glóbulos brancos no humor vítreo e aquoso. Bactérias gram-positivas são os *microorganismos* mais frequentemente isolados, particularmente os staphylococci coagulase-negativo como o *S. epidermidis.*

No que diz respeito à endoftalmite crónica pós-operatória, geralmente esta é mais insidiosa e à observação é característica a presença de placas brancas na cápsula observadas à lâmpada de fenda. O Propionibacterium acnes é o agente mais frequentemente associado a este tipo de endoftalmite.

Nas endoftalmites pós-trabeculectomia, estas podem também ser agudas, se se desenvolverem dentro de 4 semanas, ou crónicas se se desenvolverem depois deste período. Alguns pródromos associados incluem cefaleias, conjuntivite e dor supraorbitária. Ao exame objetivo é típica a presença de um infiltrado mucopurulento no local onde foi feita a trabeculectomia. Os agentes mais frequentemente isolados são semelhantes aos isolados na endoftalmite aguda pós-operatória, à exceção na sua forma

crónica, onde as espécies de streptococcus parecem ser as predominantes.

Pelo uso cada vez mais frequente de fármacos anti-VEGF e outros intravítreos, a endoftalmite secundária a este procedimento parece ser cada vez mais importante. Os sintomas geralmente surgem poucos dias após o procedimento, mas podem levar semanas a se desenvolver. Os sintomas são semelhantes aos já referidos para outros tipos de endoftalmite, não sendo necessário todos estarem presentes para ser feito o diagnóstico. Tanto os staphylococci coagulase-negativos como as espécies de streptococcus são os agentes mais frequentemente isolados.

Relativamente à endoftalmite pós-traumática, esta é uma condição rara, mas importante no contexto de lesão ocular, tendo uma incidência mais elevada se na presença de um corpo estranho. A sintomatologia geralmente estabelece-se dentro de 12 a 24 horas após o trauma podendo ser difícil a distinção dos seus sintomas e consequentemente o seu diagnóstico dado o trauma concomitante. Os *microorganismos* mais frequentemente associados são bactérias, nomeadamente o *S. epidermidis, S. saprophyticus* e as espécies de streptococcus.

Na endoftalmite endógena, esta geralmente ocorre como uma complicação secundária de uma infeção sistémica, pelo que sintomas sistémicos podem estar também associados, além dos sintomas oculares, e estes variam de acordo com a extensão e gravidade da infeção. É mais frequente uma apresentação unilateral, normalmente à direita, pensa-se que devido à proximidade e mais direta saída de sangue do coração para a artéria carótida direita. Os fungos parecem ser os *microorganismos* mais frequentemente isolados, particularmente a *Candida albicans.*

Apesar dos *microorganismos* envolvidos, a sua virulência e incidência variarem de acordo com o tipo de endoftalmite, o diagnostico, tratamento e profilaxia parecem assentar, de uma forma geral, igual para todos, ainda que com algumas particularidades.

O diagnóstico da endoftalmite é clínico e quando suspeitada, amostras devem ser obtidas de forma a isolar o *microorganismo* causador em coloração gram, culturas e por polymerase chain reaction (PCR). Amostras de humor vítreo parecem ser mais sensíveis do que as de humor aquoso. Estas podem ser obtidas através de aspiração por agulha ou através de vitrectomia. A decisão entre estas duas técnicas de recolha de amostra foi bem estabelecida no estudo EVS (Endophthalmitis Vitrectomy Study). Este foi um estudo feito no início dos anos 90 que estudou a abordagem da endoftalmite pós-

operatória e, ainda que apenas relativo à cirurgia de catarata, este tem sido a base para o diagnóstico e tratamento das endoftalmites, uma vez que é o único estudo multicêntrico, prospetivo e randomizado até à data. De acordo com o EVS, a vitrectomia como primeira abordagem pareceu ser benéfica nos doentes que à apresentação teriam apenas perceção luminosa. Nos restantes, ambos os procedimentos eram equivalentes.

Quanto ao processamento das amostras, novas técnicas de deteção de *microorganismos* têm vindo a ser desenvolvidas e parecem ser promissoras, dentro das quais se destacam a Matrix-Assisted Laser Desorption Ionization–Time of Flight (MALDI-TOF) Mass Spectrometry e o uso de sistemas de nanopartículas de DNA. A última, em particular, demonstrou ser capaz de detetar 13 espécies de bactérias em simultâneo em menos de 2 horas.

É ainda importante ter em conta o diagnostico diferencial com entidades clínicas como a Síndrome Tóxica do Segmento Anterior (STSA), retenção de lentes, hemorragia do vítreo, surtos de uveíte, entre outros, pela sua potencial semelhança clínica. Na STSA, em particular, a característica mais importante para a distinguir de endoftalmite, é o facto da primeira estar normalmente associada à formação de fibrina na câmara anterior, mas sem envolvimento do humor vítreo, envolvimento este que acontece na endoftalmite. Outras características da STSA que a permite distinguir incluem o inicio súbito (12-24h pós-operação), edema da córnea (limbus-to-limbus), alteração da iris (fixa, dilatada or pupila irregular, defeitos da transiluminação), pressão intra-ocular elevada e o facto da STSA normalmente responder ao uso de corticosteróides.

Relativamente ao tratamento, o passo mais importante é a administração direta intraocular de antibióticos. Antibióticos de largo espectro com cobertura de *microorganismo*s gram-positivos e gram-negativos devem ser iniciados após a obtenção das amostras, e subsequentemente ajustados de acordo com o antibiograma.

Normalmente, a co-administração de vancomicina (1mg/0.1mL) e ceftazidima (2.25mg/0.1mL) é a primeira linha e a co-administração de vancomicina e amicacina (0.4 mg/0.1mL) segunda linha, sendo cada fármaco diluído em 0.1mL de água esterilizada ou salina. A escolha destes fármacos prende-se com o facto da vancomicina oferecer uma cobertura de aproximadamente 100% de *microorganismos* gram-positivos e a

ceftazidima uma cobertura excelente de gram-negativos. A preferência pela ceftazidima em prol da amicacina prende-se com o risco mínimo de enfarte macular com a administração de aminoglicosídeos.

Em casos mais graves de endoftalmite pós-operatória bacteriana, pode ainda ser co-administrada dexametasona juntamente com os antibióticos intravítreos, contudo, estes devem ser evitados se houver a suspeita de endoftalmite fúngica, pelo risco de desenvolver uma endoftalmite fulminante. Se a endoftalmite aguda pós-operatória for refratária, com rápido agravamento da acuidade visual, a vitrectomia completa é fundamental para o tratamento.

No que diz respeito ao uso de antibióticos sistémicos, a sua utilidade e benefício é controverso. Contudo, na endoftalmite endogena, o tratamento da infeção de origem com antibióticos ou antifúngicos sistémicos, dependendo do agente em causa, é necessário pelo que deve ser adicionado ao tratamento de base com os antibióticos intravítreos. Nestes casos, a vitrectomia também parece ser benéfica no tratamento.

Contudo, apesar do tratamento adequado, o prognóstico a nível da acuidade visual é reservado e por isso medidas asséticas de prevenção são importantes. Dentro destas destacam-se o tratamento de patologia ocular presente previamente a qualquer procedimento ocular, por exemplo, a blefarite, uma vez associadas a uma maior carga microbiana na superfície ocular, o uso de instrumentos devidamente esterilizados, o uso de máscaras de proteção individual e a aplicação de iodopovidona. O uso de Iodopovidona é a única intervenção pré-operatória que permite a redução do risco da taxa de endoftalmites e deve ser aplicada na córnea, no saco conjunctival e na superfície periocular 3 minutos antes da cirurgia. As bactérias não desenvolvem resistência à iodopovidona e esta parece ser também eficaz contra vírus e fungos. No que diz respeito à cirurgia de catarata, a profilaxia com administração de 1mg de cefuroxime no final do procedimento parece ter benefício na redução da incidência de endoftalmites.

Por fim, ainda que muita informação se saiba relativamente a esta patologia, são precisos mais estudos para que seja possível desenvolver abordagens de diagnostico, tratamento e profilaxia melhores e mais seguras que incluam as todas as formas de apresentação desta doença.