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Endophthalmitis Prevention, Diagnostic Procedures and Treatment

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Abstract

Endophthalmitis is a severe inflammation of the inner eye's structures, caused by an exogenous or endogenous infection with microorganisms which can multiply rapidly. It occurs most frequently after intraocular surgery. Moreover, it can also be a consequence of a penetrant eye injury or a hematogenous dissemination of microorganisms. The most common pathogens of this inflammation are bacteria, next to fungi and less frequently parasites. The occurrence, severity and clinical presentation of endophthalmitis depend on the way of infection, the number and virulence of pathogenic bacteria, as well as the patient's immunity state. The type of endophthalmitis can suggest the possible causative agent. Furthermore, it can help determine therapeutic approach or antibiotics to choose. The more virulent are the causative agents, the early the symptoms and signs of endophthalmitis appear. Such types of endophthalmitis have a bad course and poor prognosis concerning visual function. In these cases the red fundus reflex is lost quite at the beginning of the disease. Patients treated with prompt vitrectomy and intravitreal injections of antibiotics have statistically better visual outcomes and less likelihood of severe visual loss.

Introduction

Endophthalmitis is a sight-threatening inflammation of the inner eye structures. It usually results from an infection or invasion of microorganisms into the eye [1-4], most often following intraocular surgery, but also, it can be generated by open eye injury or spread of infection from the cornea or other parts of the body by hematogenous routes [1,2,4-7] The most common causing agents of endophthalmitis are bacteria, followed by fungi and less frequently parasites [2,5]. The inflammatory response induced by microorganisms and their released toxins results in rapid and irreversible damage to photoreceptors or other retinal cells, and may continue even after the infection has already resolved [4].

Classification of Endophthalmitis

Endophthalmitis is classified according to the timing, way of entry of the microorganisms into the eye and the type of agents (e.g. bacteria, fungi) involved in its pathogenesis [8].

Depending on the route the microorganisms enter into the eye, two types of endophthalmitis can be distinguished:

1. Exogenous;

2. Endogenous [9].

Exogenous endophthalmitis can be further classified depending on the etiology as:

1. Postoperative endophthalmitis, which may be:

-acute

-chronic

-bleb-related

2. Post-traumatic endophthalmitis [6,10]

Exogenous endophthalmitis

This type of endophthalmitis occurs as a result of inoculation of microorganisms into the eye through a surgical, injury wound [2,3,11] or by direct spread of infection from the surrounding tissues [6].

Postoperative endophthalmitis: Postoperative endophthalmitis is the most common form of endophthalmitis [2]. It represents approximately 70% of all cases [8]. It occurs after intraocular surgery, when the entire thickness of the cornea or sclera is penetrated [2,10] and rarely after extraocular interventions such as suturing of a scleral buckle, strabismus- and pterygium- surgery or removal of corneal sutures [2,6].

About 90% of postoperative endophthalmitis occurs after cataract surgery as the most common intraocular surgery [1,2,6]. The incidence of endophthalmitis after cataract surgery varies between 0.01% and 0.08% [5]; after vitrectomy, it is between 0.03% and 0.05% [2,6]; after intravitreal injections it is between 0.01% and 0.06% [12] while that related to trabeculotomy is between 0.2% and 9.6% [6].

The origin of microorganisms that cause intraocular infections is heterogenous:

1. The patient's own ocular and periocular flora (the most common source of infection).

2. Infection of the eye or ocular adnexal structures (e.g. blepharitis, conjunctivitis, canaliculitis).

3. Contamination of the surgical instruments or materials being used during surgery (this is suspected in cases where local outbreaks have been reported).

4. Contamination of the operative field (from the air in the operating room, the flora of the skin and respiratory system of the operator and other team members) [4,5,7,10,13].

The most common agents responsible for postoperative endophthalmitis are bacteria, especially Gram-positive, which are part of the normal skin flora (e.g. *Staphylococci* and *Streptococci*) (Table 1) [4,5].

The acute form develops within six weeks after surgery, wherein the signs and symptoms in most of the patients occur within the first 2 weeks [5,6]. The chronic form develops 6 weeks or more after surgery [5,13].

(a) Acute postoperative endophthalmitis: Acute postoperative endophthalmitis is suspected in all cases with intraocular inflammation, where deviation from the typical response seen from surgical trauma exists [2]. The patient usually indicates a rapid deterioration of visual acuity, which is often accompanied by pain and signs of diffuse inflammatory reactions (red eye, hypopyon, vitritis) [2,5,7,13]. If the clinical diagnosis of endophthalmitis is made, then a fast action plan must be made, samples taken for microbiological testing and treatment commenced [5]. In the differential diagnosis, sterile intraocular inflammations should be considered, such as toxic anterior and posterior segment syndromes, uveitis due to residues from lens particles and masquerade syndrome [2,7,13]. Any time the diagnosis of endophthalmitis is suspected, close monitoring of the patient should occur [2].

Fifty percent of patients with acute endophthalmitis after cataract surgery have final visual acuity lower than 0.5, and 10% of these patients end up with visual acuity worse than 0.05 [1,7].

Types of endophthalmitis	Microorganisms	Prevalence
Acute	Coagulase-negative staphylococci	33 - 77 %
	Staphylococcus aureus	10 - 21 %
	β-haemolytic streptococci, *S. pneumoniae, S. mitis, S. salivarius*	9 - 19 %
	Gram negative bacteria (e.g. *Pseudomonas aeruginosa, Haemophilus influenzae*)	6 - 22 %
	Fungi (e.g. *Candida* spp., *Aspergillus* spp., *Fusarium* spp.)	Up to 8 %
Chronic	Propionibacterium acnes	2/3rd of cases
	Corynebacterium spp., *S. epidermidis*, Fungi	1/3rd of cases

Table 1: Common agents of postoperative endophthalmitis after cataract surgery, according to the European Society of Cataract and Refractive Surgery (ESCRS) Guidelines on prevention, investigation and management of post-operative endophthalmitis (2013) [5].

(b) Chronic postoperative endophthalmitis: Chronic postoperative endophthalmitis (after cataract surgery) appears more than 6 weeks postoperatively [2,4,5]. This form develops when microorganisms of low virulence become captured within the lens capsule [5,13].

The presenting symptoms of chronic postoperative endophthalmitis include mild progressive deterioration of visual acuity, often without accompanying pain [5-7,13]. Biomicroscopy examination usually reveals some signs of chronic or recurrent uveitis, which initially may respond to topical corticosteroid therapy, but flaring of the condition can be brought again when lower doses of corticosteroids are being used [5,6,10]. The clinical picture can be seen as anterior uveitis with mutton-fat precipitates or small hypopyon, mild anterior vitritis, whitish plaques on the capsular bag or intraocular lens (IOL), corneal edema, white infiltrates in the anterior chamber or the vitreous humor as "string of pearls" (the latter being typical of fungi) [5,7,10,13].

(c) Bleb-related endophthalmitis: Endophthalmitis after filter bleb operation is presented by blebitis and clinical picture of acute endophthalmitis. The condition may develop following trabeculotomy early after surgery or late (more than 6 weeks after the procedure); nevertheless, in both cases, it presents a clinical picture of acute inflammation [6] The most common pathogens are streptococci, Gram-negative bacteria, *S. aureus* and coagulase-negative Staphylococcus [6,7].

Post-traumatic endophthalmitis: Endophthalmitis is one of the most severe complications of open eye injury [2]. It represents 25% of all endophthalmitis cases [2,6], with incidence ranging between 3% and 30% [1,2,4,6]. Post-traumatic endophthalmitis has a poor prognosis, since only 22-42% of patients maintain visual acuity of 0.05 or more [2,6].

Risk factors for the development of endophthalmitis following an open eye injury are: contamination of wounds with dirt or soil, late primary care of wound (>24 hours), presence of intraocular foreign body, [1,2,6,7] location and extent of lacerations or rupture of the eyeball [4].

The most common pathogens of this type of endophthalmitis are *Staphylococcus* spp. and *Bacillus* spp., [1,2,7] which together cause 95% of all post-traumatic endophthalmitis [1,4,6]. Rarely, there are isolated pathogenic streptococci, Gram-negative bacteria and fungi [1,2,6,7].

Post-traumatic endophthalmitis is usually clinically manifested as acute endophthalmitis. The speed of the clinical picture development varies from few hours to few weeks [2,6].

When speculating about post-traumatic endophthalmitis, presence of intraocular foreign body should be excluded. If the vitreous body and the retina cannot be visualized, orbital CT scan should be performed. In the cases where small or tight wound exists or where primary wound care has taken place, an ultrasound should be the mainstay of the diagnostic exam [2,6].

Endogenous endophthalmitis

Also known as metastatic endophthalmitis, it occurs when pathogenic microorganisms from inflammatory lesions elsewhere in the body enter the bloodstream, and via a damaged hemato-ocular

barrier they enter the retina and the vitreous [1-3]. This form of endophthalmitis is the rarest form (5-10% of all endophthalmitis) [2], yet, it has the worst prognosis regarding visual function [3]. Only about 40% of patients having endogenous endophthalmitis maintain visual acuity better than counting fingers [1,6]. Majority of them have associated systemic disease(s) and are immunocompromised (e.g. receive systemic immunosuppressive therapy, or have cancer, AIDS) or use intravenous drugs [1-3]. The sources of infection can be anywhere in the body, frequently being seen as liver abscesses, endocarditis and urinary tract infections. The most common pathogens causing endogenous endophthalmitis are *S. aureus* and *Streptococcus* spp., but also other microorganisms such are Escherichia coli or Klebsiella, as well as microoganisms causing opportunistic infections (e.g. fungi) can be present [1,2,7]. In cases of intravenous drug abusers, the most common cause is *Candida* spp., which usually presents as chronic endophthalmitis [14,15].

Bacterial endogenous endophthalmitis is also considered an acute endophthalmitis. The symptoms and signs of systemic infection may facilitate in making the diagnosis of endogenous endophthalmitis [1].

Clinical picture of Acute Endophthalmitis

The clinical picture and the course of endophthalmitis depends on the way the infection enters the eye, the nature and virulence of the pathogenic microorganisms involved, the number of colonies at the inoculation site(s), and also speed of the condition being recognized as such [5].

Signs and symptoms of endophthalmitis are numerous and occur in a wide variety of combinations (Table 2). The patient usually undergo a rapid deterioration of visual acuity, often accompanied by pain [5,10,16]. All forms of endophthalmitis are characterized by progressive vitritis [2,6]. The mild forms are manifested with a slight inflammatory reaction, such as presence of cells in the anterior chamber and the vitreous [2]. The severe forms can cause swelling of the eyelids, severe eye injection with chemosis, corneal edema, hypopyon, featured vitritis with loss of red reflex and presence of RAPD. Focal or multifocal areas of chorioretinitis, multiple retinal hemorrhages and multiple cotton wool spots can be present as well [2,6,7,13]. Inflammatory processes can advance to panophthalmitis, but they can also cause perforation of the eyeball with orbital cellulitis and eyeball atrophy [1,5,10].

Signs/symptoms	EVS	ESCRS
Blurred vision	94%	93%
Red eye	82%	/
Pain	74%	79%
Hypopyon	75%	72%
Media haze	79%	63%
Swollen eyelids	34%	46%

Table 2: Clinical features of postoperative endophthalmitis summarized by the Endophthalmitis Vitrectomy Study (EVS) and the ESCRS Guidelines for Prevention and Treatment of Endophthalmitis Following Cataract Surgery [5,17].

The clinical picture of endophthalmitis may indicate the possible source(s) of infection and makes it easier to decide how to approach and select the proper antibiotic treatment. The more virulent the causative microorganisms are, the more rapid the development of endophthalmitis will be [1,2]. Severe inflammatory reaction is caused particularly by infection with *Streptococci, S. aureus, B. cereus* [4] and Gram-negative bacteria [1,2]. Infections caused by coagulase-negative staphylococci has less severe inflammatory reaction with better prognosis [1,2,6,18].

Diagnosis

The diagnosis of endophthalmitis is initially clinical and confirmed by microbiological cultures [5,10]. Usually, the following samples are taken for diagnostic analysis [1,5]:

1. aqueous humor sample;

2. non-diluted vitreous sample;

3. diluted vitreous sample.

The samples are then sent for Gram and Giemsa staining, as well as aerobic, anaerobic and fungal growth cultures with antibiogram. Testing with Polymerase Chain Reaction (PCR) is more sensitive than cultures, as microorganisms are detected even if they are just a few, while the result of the investigation is provided in few hours [5,7]. The weakness of this investigation is, however, the greater possibility of sample contamination [3,5].

Gram stain results are positive in 40-50% of endophthalmitis cases [7]. The vitreous cultures are positive in 69% of cases, while the aqueous humor cultures are positive in 22.5% of the cases [5]. If suspected endogenous endophthalmitis is detected, blood cultures should be obtained (preferably 2 times during the increased body temperature) or other relevant samples [1,6].

Treatment of Endophthalmitis

Acute endophthalmitis

Acute endophthalmitis is a medical emergency and requires immediate treatment [5].

The treatment consists of:

Vitrectomy: The golden standard in the treatment of acute endophthalmitis is vitrectomy with intravitreal injection of antibiotics, made no later than 2 hours after diagnosis [5].

Vitrectomy is done under general anesthesia, but also it can be performed under para- or retro-bulbar anesthesia. The procedure is not recommended for use under topical anesthesia, since it can be painful and hard for the patients to maintain compliance [5].

Intravitreal antibiotics: Combination of broad-spectrum antibiotics effective against Gram-positive and Gram-negative bacteria is usually needed [2,5,10].

The first choice of antibiotics is [5,10]:

(a) Vancomycin 1 mg/0.1 ml (active against Gram-positive bacteria);

(b) Ceftazidime 2 mg/0.1 ml (effective against Gram-negative bacteria and is not toxic to the retina).

The second choice of antibiotics is [5,7-10]:

(a) Vancomycin 1 mg/0.1 ml;

(b) Amikacin 0.4 mg/0.1 ml (effective against Gram-negative bacteria).

It should be noted that Amikacin is retinotoxic, being the option of choice in cases of hypersensitivity to ß-lactams and ceftazidime.

If any endophthalmitis is suspected to have fungal origin, in addition to the above antibiotics, it is recommended to inject amphotericin B (5-10 µg/0.1 ml) or voriconazole (100 µg/0.1 ml) to the treatment regimen [5,7]. Drugs are generally injected slowly (over 1-2 min), each of them being given separately to avoid drug precipitation [5].

Anti-inflammatory drugs: The use of systemic and intravitreal corticosteroids is controversial for the treatment of endophthalmitis, since there is not sufficient evidence of their effectiveness [5,6]. Intravitreal injection of dexamethasone reduces the early inflammatory response of bacterial endophthalmitis, without affecting the final visual acuity [2,5,6,10]. Intravitreal administration of dexamethasone is at concentration of 0.4 mg/0.1 ml [2,5].

Intravitreal or systemic use of corticosteroid is contraindicated in case of fungal endophthalmitis [5,10]. Use of topical corticosteroids is part of the standard post-operative therapy, as it inhibits the inflammatory response and reduces secondary tissue damage [2,4].

Systemic antibiotics: A key to a successful treatment of endophthalmitis is the use of intravitreal antibiotics. Besides those, systemic antibiotics can be used as well [4,5]. Initially, broad-spectrum antibiotics are being given for endophthalmitis treatment, which can later be changed according to results obtained by the antibiogram. The antibiotic of first choice is usually the one which has been already administered intravitreally; the therapeutic intravitreal concentration of the antibiotic can be maintained for longer periods, due to a reduced concentration gradient across the hemato-ocular barrier [5].

Systemic antibiotic treatment usually lasts 10 days [10]. In the case of endogenous endophthalmitis, the source should be sought after and treated appropriately [2,3,7].

Endophthalmitis caused by fungi, in addition to intravitreous antifungal injections, also requires several weeks of long systemic treatment with fluconazole or vorikonazole [7].

Topical therapy: Topical therapy is initiated right after the diagnosis is made. It can be prescribed according to the following rules:

(a) Use of an antibiotic that achieves therapeutic concentrations in the anterior segment should be initiated [5,6,10]: a broad spectrum antibiotic such as fluoroquinolones (moxifloxacin [6] or ciprofloxacin) or fortified antibiotics can be used [10];

(b) Corticosteroids (e.g. dexamethasone drops) [5,6,10];

(c) Mydriatics to prevent the formation of synechiae [5].

Monitoring of the patient: The clinical response to the treatment is assessed after 6 to 12 hours [5]. Often a temporary deterioration in the clinical picture is seen before it starts improving [5,6]. After 48 to 72 hours, a decision needs to be made whether intravitreal antibiotics should be re-administered. The interval depends on the half-life of the antibiotic being used and the clinical picture of the endophthalmitis [5,6,10]. If the signs of inflammation (e.g. hypopyon, fibrin, vitritis, etc.) subside, further intravitreal therapy is not necessary. However, if the situation is not improving or is getting worse, intravitreal antibiotic use must continue [5,10]. In most cases, it is required that a single intravitreal injection is re-injected (according to the study by EVS, 7% of patients were re-injected), while in case of fungal endophthalmitis usually several applications of intravitreal injections may be necessary [5].

Chronic postoperative endophthalmitis

In this form of endophthalmitis, the diagnostic and treatment approach is less aggressive. It starts by sampling of aqueous humor for use in microbiological culture and PCR examination [5,13], followed by prescription of oral therapy such as clarithromycin 500 mg/12 hours for 2-4 weeks, or moxifloxacin 400 mg/24 hours for 1 week. Both antibiotics penetrate well into the eye and are effective against biofilm formation [5].

If the initial treatment is not effective, vitrectomy with posterior capsulotomy and application of appropriate intravitreal antibiotics should be performed. Antibiotics for intravitreal and systemic administration are selected according to the antibiogram results, if such are indeed available. Otherwise, broad-spectrum antibiotics are the treatment of choice at this stage [5].

Where not sufficient effect is achieved by the above protocol, re-operation and explantation of the intraocular lens needs to be performed [5,6,13].

In cases of suspected chronic endophthalmitis caused by fungi, intravitreal injection of antifungal drugs in addition to a systemic antifungal therapy should be administered [10] (as described above).

Prevention of Postoperative Endophthalmitis

Measures to prevent postoperative endophthalmitis are directed primarily to the reduction of microbial flora of the eye surface, eyelids and lashes with proper preparation of the operative field, maintaining its sterility during the procedure and preventing infection until complete epithelialization of the wound has been achieved.

Preoperative antisepsis

The number of bacteria on the surface of the eye is most effectively reduced with a precise and thorough preoperative cleaning of the periocular skin with 5-10% povidone iodine; 5% povidone iodine is also instilled in the conjunctival sac [5,10,13] and it should remain on the surface of the eye for at least 3 minutes [5]. In case of allergic reactions to povidone iodine, 0.05% chlorhexidine can be used instead [5,10,13]. So far, there is no clear evidence that preoperative use of topical antibiotics reduces the incidence of post-operative endophthalmitis [5,13].

When draping the periorbital area, the eyelashes and the margins of the eyelids must be properly covered. This reduces the possibility of operative field contamination [10,13].

Intraoperative measures

During surgery, the sterility of the operative field should be maintained with established antisepsis measures: use of sterile instruments and other materials during the procedure, wearing face masks, surgical coat and also proper airflow within the operating room [5,10]. It is recommended to use disposable instruments. For each intervention, a new infusion bottle should be used [5]. Particular

attention should be paid to the incision wound construction. Risk is higher in cataract surgery with clear cornea incision when compared to scleral tunnel incision [5,10,19].

The incidence of endophthalmitis after cataract surgery is reduced by intracameral injection of broad-spectrum antibiotics at the end of the operation. For that purpose, the ESCRS study showed that prophylactic use of intracameral cefuroxime (1 mg/0.1 ml) reduces the incidence of endophthalmitis approximately 5 times. Good results have also been shown with using intracameral vancomycin (1 mg/0.1 ml) as well.

Postoperative measures

Postoperative topical antibiotic prescription in order to reduce the possibility of microbial inoculation through operative wound is recommended for at least one week.

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References

1. Coburn PS, Callegan MC (2012) In: Rumelt S. Advances in Ophthalmology. Rijeka: InTech, Endophthalmitis, pp: 852
2. Kernt M, Kampik A (2010) Endophthalmitis: Pathogenesis, clinical presentation, management, and perspectives. Clin Ophthalmol 4: 121-135.
3. Connell PP, O'Neill EC, Fabinyi D, Islam FMA, Buttery R, et al. (2011) Endogenous endophthalmitis: 10-year experience at a tertiary referral centre. Eye 25: 66-72.
4. Callegan MC, Engelbert M, Parke DW II, Jett BD, Gilmore MS (2002) Bacterial Endophthalmitis: Epidemiology, Therapeutics, and Bacterium-Host Interactions. Clin microbiol rev 15: 111-124.
5. Barry P, Cordovés L, Gardner S (2013) ESCRS Guidelines for Prevention and Treatment of Endophthalmitis Following Cataract Surgery: Data, Dilemmas and Conclusions. Dublin, Ireland, European Society of Cataract and Refractive Surgeons.
6. Lemley CA, Han DP (2007) Endophthalmitis A Review of Current Evaluation and Management. Retina 27: 662-680.
7. Durand ML (2013) Endophthalmitis. Clin Microbiol Infect 19: 227-234.
8. Huang JJ, Gaudio PA (2010) Ocular inflammatory disease and uveitis manual: diagnosis and treatment. Philadelphia: Wolters Kluwer/ Lippincott Williams & Wilkins Health.
9. Ojaimi E, Wong DT (2013) Endophthalmitis, Prevention and Treatment. In: Zaidi FH. Cataract Surgery Rijeka: InTech 265-284.
10. Ismail M (2014) Clinical practice guidelines. Management of post-operative infectious endophthalmitis. Ministry of health Malaysia; Academy of medicine.
11. Vidyashankar B, Arora S, Singal R, Shahnawaz K, Motwane SS (2001) Medical treatment of endophthalmitis. Journal of the Bombay Ophthalmologists' Association 11: 47-50.
12. Casparis H, Wolfensberger TJ, Becker M, Eich G, Graf N, et al. (2014) Incidence of presumed endophthalmitis after intravitreal injection performed in the operating room. A Retrospective Multicenter Study. Retina 34: 12-17.
13. Packer M, Chang DF, Dewey SH, Little BC, Mamalis N, et al. (2011) Prevention, diagnosis, and management of acute postoperative bacterial endophthalmitis. J Cataract Refract Surg 37: 1699-1714.
14. Connel PP, O'Neil EC, Islam FMA, Buttery R, McCombe M, et al. (2010) Endogenous endophthalmitis associated with intravenous drug abuse: seven-year experience at a tertiary referral center. Retina 30: 1721-1725.
15. Patel SN, Rescigno RJ, Zarbin MA, Langer P, Bhagat N (2014) Endogenous endophthalmitis associated with intravenous drug abuse. Retina 34: 1460-1465.
16. Schlossberg D (2008) Clinical Infectious Disease. Cambridge: Cambridge University Press.
17. Bandello F, Battaglia Parodi M (2012) Surgical Retina, ESASO course series. Basel, Karger Publishers.
18. Saer JB (1998) Vitreo-retinal and uveitis update: proceedings of the 47th Annual Symposium of the New Orleans Academy of Ophthalmology, New Orleans, LA, USA, Hague: Kugler Publications.
19. Cao H, Zhang L, Li L, Lo S (2013) Risk factors for acute endophthalmitis following cataract surgery: a systematic review and meta-analysis. PLoS One 8: e71731.