ENDOGENOUS ENDOPHTHALMITIS

RODICA LASCU[1]

[1]*Dr Lascu Ophtalomology Private Office Sibiu*

Keywords:
endogenous bacterial endophthalmitis, fungal endophthalmitis, endophthalmitis with Aspergillus

Abstract: *Endogenous endophthalmitis is an ophthalmological emergency that may have severe complications that endanger visual acuity. It is often a diagnostic challenge because it can manifest at any age and is associated with a number of favoring factors. The micro-organisms associated with this disease vary across a broad spectrum. Depending on the severity of the disease, both interventions can be used: medical and surgical. Due to the rarity of this disease, there are no guidelines in the literature for the optimal treatment of these patients.*

INTRODUCTION

Endogenous endophthalmitis (EE) results from the hematogenous spread of micro-organisms from distant focals. EE represents about 2-8% of all cases of endophthalmitis. Unlike exogenous endophthalmitis, demographic data, treatment options in EE patients have not been extensively studied (1,2)

The first case of bacterial EE was published in 1856. Subsequently, a study of approximately 335 cases of bacterial EE was published in 2003. There were no major reviews in the literature that included all infectious etiologies, including both bacterial and fungal etiologies.(2)

The etiology of EE is multifactorial, and the list of causes is very large, with significant geographic variations. Both bacterial and fungal agents are mentioned in the literature as potential EE agents in the developed world. However, fungal etiology is mentioned in the majority of cases. The bodies responsible for bacterial EE differ depending on the geographical location. In the developed countries, Gram-positive organisms (*Streptococci and Staphylococci*) dominate the infection, while gram-negative organisms are more common in the Asian population. Asian studies reported causative fungi agents in approximately 11.1-17.54% of all cases of EE, the rest being attributed to bacterial causes.(2)

The *risk factors* for this disease are: recent hospitalization, diabetes, urinary tract infections, immunosuppression (especially associated with malignancy, neutropenia and HIV (human immunodeficiency virus)), intravenous drug abuse and catheters. Liver abscesses have been observed to be associated with EE, especially those caused by Gram negative bacilli, such as Klebsiella pneumonia. Infectious endocarditis is another important risk factor commonly associated with EE in the Western countries. Various causes of transient bacteria, such as routine colonoscopy, can also lead to EE. Patients with chronic pulmonary aspergillosis**.** are at an increased risk of developing EE.

Neonatal endogenous endophthalmitis deserves a special mention. Newborns with candidemia, bacteremia, and retinopathy of prematurity and low birth weight have a significant risk for EE development. Causes are bacteria of Streptococcus species, especially S. agalactia, gram negative rods such as Klebsiella or Pseudomonas and fungi, including Candida species. A recent report suggested a decrease in the incidence of neonatal EE in the developed world.(2)

Pathophysiology: Endogenous endophthalmitis results from metastatic spread from the primary site of the infection. Most frequently, the infection reaches the eye through the posterior segment vasculature. The right eye is more frequently involved, probably due to the more direct pathway through the right carotid artery. Direct spreading can also occur in cases of central nervous system infection through the optic nerve. Unlike post-operative endophthalmitis and post-traumatic endophthalmitis, endogenous endophthalmitis is most likely due to a septic embolism that enters the posterior segment vascularization and acts as a dissemination focal in the surrounding tissues after passing the blood-brain barrier to determine microbial proliferation and inflammatory responses within these tissues. The infection then extends to the coroid, retina, into the vitreous cavity and then into the anterior chamber of the eye.(2)

Clinical characteristics: EE diagnosis can be difficult due to the variability of clinical signs and symptoms.

Table no. 1. Signs suggestive of endogenous endophthalmitis (2)

Positive	**Possible**	**Probable**
Abscesses of uveal tissue	Hypopyon ≤ 1,5 mm	Conjunctival injection / chemosis
Hypopyon ≥ 1,5 mm	Vitreous opacity, but not visible exudates	Inflammation of the anterior chamber, but not hypopyon
Glassy exudates	Discrete, non-necrotic, focal corioretin lesions	Absence of vitreous opacity
Visible arteriolar septic embolism	Optic neuritis	Corneal edema
Necrotizing retinitis	Intra-retinal haemorrhages	fever
Perivascular haemorrhages with infiltrate inflamator	White reflex of the newborn	
panophtalmia	Scleritis	
Corneal infiltrates or ulcers		

Patients may experience decreased vision, palpebral edema, conjunctival hyperaemia, pericreatic congestion, pain, photophobia, vitreous flocculation, hypopyon. Other signs may

[2]Corresponding author: Rodica Lascu, Aleea Infanteriştilor, Bloc I, Scara B, Etaj III, Ap. 25, Sibiu, România, E-mail: lascughrodica@yahoo.com, Phone: +40720 547341

Article received on 17.02.2017 and accepted for publication on 25.05.2017
ACTA MEDICA TRANSILVANICA June 2017;22(2):78-80

also be present, such as: corneal edema, presence of iridium nodules, pupillary deformation secondary to synechia formation.(2)

The diagnosis is based on anterior chamber paracentesis and vitrectomy with culture of vitreous and aqueous humor specimens, as well as Giemsa and Gram staining if fungal organisms are suspected. Blood count or tests made from other body fluids should be corroborated to confirm the diagnosis and to determine the treatment.(3)

Treatment of endogenous bacterial endophthalmitis:

1a. *Endogenous bacterial endophthalmitis:*

Treatment consists of intravitreal antibiotics by vitrectomy, and if necessary, associated antifungal therapy. Antibiotics are administered immediately, empirically, in the form of antibiotic associations, or targeted, according to cultures results. The current therapeutic recommendations indicate the following antibiotics: Vancomicine (for gram positive); Aminoglicoside-Amikacin (for gram negative); Cefalosporine of the third generation, Ceftazidim. Instead of Ceftazidime, Amikacin may be administered to patients with beta-lactam allergy but it should be used with caution because of the increased risk of retinal toxicity, such as macular infarction; *Mycobacterium tuberculosis* may present bilateral endophthalmitis and inflammation of the sclera.(2) To exclude Bacilus-Clindamicin species (1,3), broad-spectrum intravenous antibiotics, Vancomicine, Aminoglicoside-Amikacin, Cefalosporine Iii-Ceftazidim are used. Regarding the periocular antibiotics; cycloplegics; topical steroids; Vitrecomy for virulent bacteria, if necessary association with antifungal and stenic therapy (sometimes 6 weeks or more).(1,4)

The incidence of drug resistance is high in other stages of the disease. There have been reports of enterococcal resistance to Vancomycin in patients with endophthalmitis.(3)

Intravitreal fluoroquinolones, especially Moxifloxacin, are considered as alternatives to Vancomycin and Ceftazidim because of their broad spectrum, which allows the gram-positive and negative bacteria to be covered by a single agent. Data suggests that these agents can be used topically or systemically rather than intravitreally. Due to the wide use of these substances in the prophylaxis and treatment of superficial eye infections, their resistance is subject to many concerns. Therefore, in the case of fluoroquinolone administration, these should be prescribed along with a medication that most likely covers the gram-positive organisms.(2,3)

Table no. 2. The pharmacotherapy of endogenous bacterial endophthalmitis. *VSSA* staphylococcus aureus sensitive to Vancomycin, *VRSA* staphylococcus aureus resistant to Vancomycin

Drug	The intravitreal dose
A. Gram-positive bacteria (including VSSA)	
Vancomicyn	1 mg / 0,1 ml
Cefazolin	2,25 mg / 0,1 ml
B. Gram-positive bacteria (including VRSA)	
Daptomycin	200 mg / 0,1 ml
Quinupristin / dalfopristin	0,4 mg / 0,1 ml
C. Gram-negative bacteria	
Ceftazidime	2,25 mg / 0,1 ml
Amikacin	0,4 mg / 0,1 ml

1b. *Endogenous fungal endophthalmitis*

1b1. Endophthalmitis produced by candida that can cause corioretinic damage that does not affect the vitreous body and can benefit from oral antifungal treatment: Triazol; Fluconazol; Voriconazol. In the case of endophthalmitis with the vitreous body, the following are indicated: 1. Vitrectomy by pars plana; 2. Antifungal agents, intravitreal amphotericine B, Voriconazole with or without Dexametazone. 3. In the more severe infections, i.v. amphotericin B antifungal is also used with or without Flucitosine 4. Caspofugina - new antifungal in the echinocondium class, with therapeutic activity against the candida and aspergillus species. 5. Hicafungin i.v. for treatment in Candida. 6. Systemic administration of Amphotericin B, Caspofugin associated with oral treatment with Voriconazole, Fluticosin, Fluconazole, Rifampicin.(2,4)

1b2. Endophthalmitis with aspergillus-requires aggressive treatment with: 1. therapeutic and diagnostic pars plana vitrectomy combined with intravitreal injections of Amfotericine B or Voriconazole and Corticoids iv. 2. Most of these patients have disseminated aspergillosis and require systemic treatment associations with oral treatment Amphotericin B, Voriconazole, Caspofungin; 3. The following can also be used: Itraconazole, Micafungin, Flucitozin.(1,4)

1b3. Endophthalmitis with cryptococcosis-requires oral treatment with Amfotericine B and oral Flucitozin to stop the progression of the disease.(4)

1b4. Endophthalmitis with coccidioidomycosis: 1. They can be treated orally with Fluconazol, Itraconazole; 2.For unfavorable evolution or vital locations - Fotericina B; **3.** Sometimes vitrectomy is required through pars flat and intravitreal injection of Amfotericine B and Voriconazol. 4. If systemic disease is present, i.v. Amphotericin B and voriconazole are associated for long time.(4)

Table no. 3. Pharmacotherapy of endogenous fungal endophthalmitis and their sensitivity (2)

Drug	Intravitreal dose	Systemic dose	Candida	Aspergillus	Other
A. Polyene					
Amphotericin B	5 μg/0.1 ml	0.5–0.7 mg/kg (IV)	++	+	
B. Imidazoles					
Miconazole	25–50 μg/0.1 ml	–	+	+	
Itraconazole	5 μg/0.05 ml	200–400 mg/day (orally)	+	+	
		200 mg/zi (IV)			
Voriconazole	50–200 μg/0.1 ml	200 mg de twice a day (oral)	+++	++	Fusarium +
		3–6 mg/kg (IV) twice a day			
C. Pyrimidine					
5-Flucytosine	2.25 mg/0.1 ml	25– mg/kg/day	−	+	
D. Echinocandins					
Caspofungin	–	50 mg/day	+	+	

Patients with endogenous endophthalmitis usually suffer from an older, chronic condition such as diabetes, cancer, organ transplantation, sepsis associated with intravenous therapy, and AIDS. Treatment aims at alleviating or eliminating the underlying problem, as the source usually originates elsewhere in the body. The administration of systemic and antifungal antibiotics is essential in treating this condition. In the literature, ocular globules with endogenous fungal endophthalmitis showed better results than in cases of endogenous bacterial endophthalmitis.(3)

Pars plana vitrectomy (PPV)

PPV is commonly used in EE treatment. It is recommended in bacterial endophthalmitis, or with Candida, Aspergillus. PPV serves both diagnostic and therapeutic purposes. An intravitreal injection of drugs may be given during the operation. The decision on vitrectomy is usually based on the judgment of the clinician.(2)

Better visual results were reported in cases that experienced early vitrectomy. The decision in early vitrectomy was also associated with a decrease in the incidence of retinal detachment, evisceration or enucleation. Sato et al. have recommended the use of vitrectomy for Candida EE before stage IV according to Ishibashi's classification.(5) In the case of bacterial EE, vitrectomy is generally performed when there is no response to intravitreal antibiotics within 48 hours. Yoon et al.,

Ishii et al. have suggested aggressive treatment, including early vitrectomy for Klebsiella EE.(6) On the other hand, Sheu et al. have not found any association between vitrectomy time and visual outcome in Klebsiella EE.(7) However, they have still suggested the use of surgery, especially in patients with anterior chamber inflammation, who have not responded well to intravitreal antibiotics.

The role of corticosteroids: data on the use of steroids in endophthalmitis are limited and the results of the studies are contradictory. Therefore, judicious use of corticosteroids is recommended.(2)

Complications of endogenous endophthalmitis may be serious. If the diagnosis of systemic infection is not established, the patient may develop septicemia and may even die. Complications such as cataract development, retinal detachment, supracoaral haemorrhage, vitreous haemorrhage, hypotonia, and fistula bulb may occur in most severe cases.(3)

Prognostic: Endogenous endophthalmitis has reserved prognosis. The prognosis is directly related to the affected organism and the systemic health status of the patient.(3)

Conclusions:

EE is an ophthalmic emergency that requires prompt diagnosis and management. The main challenges in EE management are early identification and provision of adequate drug concentration in the vitreous cavity. It may be possible to administer the direct intravenous antibiotics. Systemic therapy is used to treat the infection focal that causes metastatic spread of the germ into the ocular cavity. In mild cases of EE, systemic therapy is the main pillar of treatment. However, in severe cases, systemic therapy is an adjuvant to more aggressive intravitreal drug administration. PPV plays a diagnostic and therapeutic role in EE management.

REFERENCES

1. American Academy of Ophthalmology. Intraocular Inflammation and Uveitis. BCSC Basic and Clinical Science Course. 2012-2013; Section 9; p. 271-280.
2. Dumitrache M, Potop V. Endoftalmitele; Tratat de Oftalmologie-vol II-Editura Universitară Carol Davila, Bucureşti. 2012;18:879-892.
3. Dumitrache M, Pienaru M. Tratamentul în endoftalmite; Tratamentul chirurgical şi tratamentul laser în boli oculare; Editura Universitară Carol Davila, Bucureşti; 2014;9:375-391.
4. Ali Sadiq M, Hassan M. Agarwal A, şi colab. Endoftalmita endogenă: diagnostic, management şi prognostic; Journal of oftalmic inflamaţie şi infecţie. 2015;5:32.
5. Sato Y, Miyasaka S, Shimada H. Prognosis of endogenous fungal endophthalmitis and utility of Ishibashi's classification. Jpn J Ophthalmol. 2001;45(2):181–186. doi: 10.1016/S0021-5155(00)00355-5. [PubMed] [Cross Ref].
6. Ishii K, Hiraoka T, Kaji Y, Sakata N, Motoyama Y, Oshika T. Successful treatment of endogenous Klebsiella pneumoniae endophthalmitis: a case report. Int Ophthalmol. 2011;31(1):29–31. doi: 10.1007/s10792-010-9387-7. [PubMed] [Cross Ref].
7. Sheu SJ, Kung YH, Wu TT, Chang FP, Horng YH. Risk factors for endogenous endophthalmitis secondary to klebsiella pneumoniae liver abscess: 20-year experience in Southern Taiwan. Retina. 2011;31(10):2026–2031. doi: 10.1097/IAE.0b013e31820d3f9e. [PubMed] [Cross Ref].