Prognostic factors and imaging procedures in postoperative endophthalmitis and in severe eye injuries

Doctoral thesis

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1. List of abbreviations

ANOVA	Analysis of variance
BETTS	Birmingham Eye Trauma Terminology Scale
CCI	Clear Corneal Incision
Ch	Choroid
ChCap	Choriocapillary
CRT	Central Retinal Thickness
ECCE	Extracapsular cataract extraction
ECM	Extracellular Matrix
EDI	Enhanced depth imaging
ETDRS	Early Treatment Diabetic Retinopathy Study
EVS	Endophthalmitis Vitrectomy Study
FLA	Fluorescein Angiography
FT	Foveal Thickness
GCL + IPL	Ganglion Cell Layer and Internal Plexiform Layer
HEIR	Hungarian Eye Injury Register
Hz	Herz (oscillations / sec.)
ICCE	Intracapsular cataract extraction
ILM	Inner Limiting Membrane
INL	Inner Nuclear Layer
IOFB	Intraocular foreign body
IS/OS	Inner Segment / Outer Segment
ISOT	International Society of Ocular Trauma
LC	Lamina cribrosa
logMAR	Logarithm of the Minimum Angle of Resolution

MV	Macular Volume
OCT	Optical Coherence Tomography
ONH	Optic nerve head
ONL	Outer Nuclear Layer
OPL	Outer Plexiform Layer
OTS	Ocular Trauma Score
PEWT	Posterior eye wall thickness
POE	Postoperative Endophthalmitis
PPV	Pars plana vitrectomy
PVD	Posterior Vitreous Detachment
RAPD	Relative afferent pupillary defect
RNFL	Retinal Nerve Fiber Layer
RPE	Retinal Pigment Epithelium
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SMD	Serous Macular Detachment
TD-OCT	Time Domain Optical Coherence Tomography
WHO	World Health Organization

2. Introduction and review of the literature

2.1. Introduction

Postoperative endophthalmitis is still one of the most dangerous complications after cataract surgery. With pars plana vitrectomy performed at an early stage and with the standard procedures recommended by the Endophthalmitis Vitrectomy Study (EVS) this severe inflammation of the eye can be treated successfully. To better understand the structural changes in post cataract endophthalmitis we need imaging data about the changes in vitreous cavity and other parts of the posterior eyewall. Therefore, a large retrospective evaluation of ultrasonographic data would provide more information about changes in the eye due to postoperative endophthalmitis. The structural changes in the retina and choroid in different degenerative, proliferative and inflammatory diseases of the eye have been studied and described, however, it is still unknown, how postoperative endophthalmitis after cataract surgery influences the microstructure of the retina and choroid after full recovery from this severe complication. Otherwise it is known, that choroidal thickness changes after posterior uveitis or after filtering microsurgery in glaucoma. In addition, the presence of structural retinal and choroidal changes due to post cataract endophthalmitis may help to predict the long term clinical outcomes after performed vitrectomy as first choice treatment. The advantage of OCT and ultrasound imaging is their non-invasive nature with minimal risk for the patients.

Endophthalmitis is also a severe complication after open globe injuries with intraocular foreign bodies. Accurate imaging procedures are fundamental for the diagnosis, treatment and the prognosis of these severe eye injuries. Therefore, the examination of clinical data using a specific classification of the eye injuries would provide information about clinical outcomes and help to establish a prognosis. Imaging examinations are fundamental for the location of intraocular foreign bodies. Numerous authors, listed above, have shown different imaging procedures and established important recommendations for the early management of these injuries in order to guarantee the best possible postoperative outcomes. CT, x-ray radiography, ultrasonography and OCT are standard procedures in the diagnostics and clinical management of eye injuries with IOFBs. Especially advanced technologies in CT such as CT volumetry may help to better localize IOFBs and help to plan the surgical treatment of these open globe injuries.

In the last decade, imaging technologies in ophthalmology have undergone an enormous development and thus provide an indispensable help for the management of postoperative endophthalmitis and open globe injuries with intraocular foreign bodies.

2.2. Review of the literature

2.2.1. Postoperative Endophthalmitis (POE)

2.2.1.1. Etiology

Endophthalmitis is the most severe inflammation involving both the anterior and posterior segments of the eye with different etiologic causes. Despite advances in prophylaxis and surgical treatment techniques, endophthalmitis remains a devastating complication of cataract surgery [1]. The most common reason for the induction and progression of an endophthalmitis is the spreading of bacteria deriving from a local infection or from a systemic infection disease [2]. The pathway for the transmission of the infection to the inner parts of the eye leads to the classification of etiology of endophthalmitis: after eye surgery (postoperative), after open globe injuries of the eye (posttraumatic), following an infection of the surface of the eye (e.g. corneal ulcer) and through endogenous pathways (haematogenous or lymphogenous). Other types of endophthalmitis are sympathetic ophthalmia, phacoanaphylactic endophthalmitis, conjunctival filtering bleb–associated, non-infectious and sterile endophthalmitis [3], but they will not be the main point of interest in this doctoral thesis. The most common type is postoperative endophthalmitis (POE) [4,5]. Cataract surgery seems to be the leading surgery type that causes postoperative endophthalmitis. It also seems that complications during cataract surgery as posterior capsule rupture or short clear corneal wound or eyes that had undergone an anterior vitrectomy during cataract surgery or a limbal incision due to astigmatism have a higher risk for developing post cataract endophthalmitis [6]. The Endophthalmitis Vitrectomy Study (EVS) demonstrated that most isolates causing clinical endophthalmitis are introduced into the eye from the patient's conjunctival flora, but also the peri- or intraoperative introduction of microbial organisms into the eye either from the patient's normal conjunctival and skin flora or from contaminated instruments can lead to this severe inflammation of the eye.[7]

In a large retrospective study conducted in Nijmegen, Netherlands, bacterial cultures (total 250 cases) showed bacterial growth in 166 cases (66.4%) [8]. Out of these 166 cultures, 89 (53.6%) revealed gram-positive coagulase-negative, 63 (38.0%) other gram-positive, 10 (6.0%) gram-negative, and 4 (2.4%) polymicrobial cultures. In another retrospective study, Lalwani et al.[6] showed that in the majority of endophthalmitis cases following cataract surgery there are coagulase negative staphylococcus species (68%), followed by staphylococcus aureus (7%) and streptococcus species. Fungal POE is very rare, the reported incidence rate of presumed acute fungal endophthalmitis ranges from 0.10% to 0.16%, but the clinical signs could be very devastating for the eye structures [9;10].

2.2.1.2 Epidemiology

Epidemiologic studies show that POE is the most common type of endophthalmitis (65-90%) [8]. Different epidemiological studies show that the incidence of this complication after cataract surgery is seldom and more seldom than in other open globe surgeries (e.g. corneal transplantation), but because of the high surgical frequency it has to be considered a very important clinical finding [12]. The incidence of endophthalmitis after pars plana vitrectomy is 0.046% to 0.07% [4; 13; 14]. The incidence may depend on the surgical procedure. The use of clear corneal incisions technique during cataract surgery has increased from approximately 5% in 1993 to 72% in 2003, and continues to increase annually [15; 16]. Whether the incidence of endophthalmitis has increased after the transition to clear corneal cataract surgery has been debated. Reported incidence rates ranged between 0.05% and 0.68% [17; 18]. In 1998, Aaberg et al., described in a retrospective study over 10 years the overall incidence of acute onset postoperative endophthalmitis within 6 days with 0.093 % of all cases after intraocular surgery [13]. Other studies show a prevalence of postoperative endophthalmitis of 0.04-0.7 % after cataract surgery, whereas after secondary IOL implantation with scleral fixation it is approximately 0.27%- 0.4% [15]. In 2014, Rudnisky et al. Showed similar results in a retrospective study over 8 years. They found an overall incidence of 0.03 % over 8 years [19]. Du DT et al. [12] also showed an incidence of 0.06-0.2% of endophthalmitis after cataract surgery. Other risk factors for postoperative endophthalmitis and their incidence include penetrating keratoplasty (0.11% to 0.18%), combined penetrating keratoplasty and cataract surgery (0.194%), and glaucoma filtering procedures (0.06% to 1.8%) [13; 20] wound leak/dehiscence, inadequately buried sutures, suture removal and vitreous incarceration in the surgical wound. The reported rate of endophthalmitis after intravitreal injection of anti–vascular endothelial growth factor (anti-VEGF) agents is 0.02% [21].

2.2.1.3 Pathophysiology and clinical features

Once clinical infection appears, damage to ocular tissues is believed to occur due to the direct effects of bacterial replication as well as the initiation of a fulminant cascade of inflammatory mediators. Endotoxins and other bacterial products appear to cause direct cellular injury, by eliciting cytokines that attract neutrophils, which enhance the inflammatory effect [22, 23]. In most cases bacteria could be isolated from vitreous specimen gained during vitrectomy. Depending on the onset of the inflammation, different types can be classified: Typically, patients present within 1 week of intraocular surgery in the case of acute postoperative endophthalmitis. We speak about subacute postoperative endophthalmitis if the inflammation occurs within 6 weeks, and delayed-onset or chronic if it happens after 6 weeks. The clinical presentation depends on the route of entry, the infecting organism, and the duration of the disease. Signs of acute postoperative endophthalmitis are moderate to severe deep eye pain, red eye and decreased vision, conjunctival hyperemia, hypopyon till 80%, pupillary fibrin membrane (80%), dense vitritis (4+, 100%) [11] and lid swelling within days after cataract surgery or secondary lens implantation [15, 6]. However, sometimes retinal detachment may be present at the time of diagnosis of endophthalmitis, or it may develop after treatment. The incidence of retinal detachment after treatment is estimated to be between 10% and 16%. [24]. For the diagnosis of endophthalmitis, ultrasound examination is fundamental and a very specific and sensitive method especially in acute onset POE and for the follow-up of this severe infection [25; 26; 27].

2.2.1.4. Prevention, treatment and prognosis

The prevention of POE primarily consists of the decrease and control of the intraoperative risk factors and the reduction of the pathogen load on ocular surface. Risk factors include inadequate eyelid/conjunctival disinfection, prolonged surgery (longer than 60 minutes), vitreous loss, use of prolene haptic IOLs, and inapparent or unplanned ocular penetration during ocular surface surgery [28]. Inadequate draping of the lids and lashes away from the surgical site has been mentioned as a possible risk factor by some authors [29; 30]. The use of 5% povidone-iodine solution in the conjunctival fornices has been shown to not only reduce bacterial load [31; 32], but also to decrease the incidence of culture-positive endophthalmitis.

There are different guidelines for the prevention of post cataract endophthalmitis. In 2006, the ESCRS Endophthalmitis Study Group published guidelines to reduce the risk of POE by using intracameral Cefuroxime at the end of the cataract surgery [33]. After the introduction of the ESCRS protocol, a comprehensive retrospective study of the incidence of POE showed strong evidence of the utility of cefuroxime as prophylaxis [34]. The use of intracameral cefuroxime at the end of the surgery significantly decreased the acute onset of postoperative endophthalmitis. Other studies support this effort and also showed the socioeconomic benefit of this procedure [35]. A comparison study between subconjunctival injections of gentamycin and vancomycin and gentamycin added to the irrigating solution showed that the efficacy for the prevention of POE is better in the mentioned second group [36]. Other studies also showed an effective preventive influence of the postoperatively use of fluorochinolons but also detected a higher risk for developing postoperative endophthalmitis after the use of timolol at the end the surgery [19]. Pijl et al [8] describe in a large retrospective study that vitreous biopsy with intravitreal antibiotics injection was performed in 225 (90.0%) of 250 post cataract endophthalmitis cases. Primary vitrectomy with intravitreal antibiotics was only performed in 10% of all cases. For the antibiotic treatment of post cataract endophthalmitis, most of the studies [8; 6] used intravitreal vancomycin for coverage of gram-positive bacteria as per recommendations in the literature [3].

The efficacy of the treatment of POE depends first of all on the early recognition of the clinical presentations, and the timing of therapy is an important factor for final clinical results (visual acuity, morphological recovery). It is helpful to distinguish “acute” from "chronic" presentations in determining the management plan [3]. Factors influencing treatment outcome after post cataract endophthalmitis are visual acuity at presentation, bacterial culture results, and the type of treatment. There is no consensus on whether a primary vitrectomy should be performed as initial treatment for endophthalmitis after cataract surgery [37]. The EVS evaluated the role of immediate pars plana vitrectomy (PPV) versus intraocular antibiotic injection and systemic antibiotics in the treatment of acute postoperative endophthalmitis. As a result, the Endophthalmitis Study Group recommended vitrectomy as first choice in cases of fulminant endophthalmitis or in cases where a rapid progression of the endophthalmitis could endanger the eye and cause severe vision loss for the patient [33]. Later the Endophthalmitis Study Group reported that the use of clear corneal incisions (CCIs) compared to scleral tunnels and the use of silicone intraocular lens (IOL) optic material compared to acrylic were associated with a higher risk for the development of acute postoperative endophthalmitis [38].

The prognosis in endophthalmitis is dependent on culture results (better prognosis for culture-negative cases), time of onset postoperative endophthalmitis (better prognosis for late-onset POE), and the virulence of the pathogen. The prognosis for patients with concomitant retinal detachment depends on the virulence of the pathogen. Successional, virulent organisms are associated with a poor visual and anatomic outcome. Typically, the worst outcomes are seen in infections with Streptococcus species, gram-negative organisms, and Bacillus species. Foster et al. showed [39] that 75% of patients with endophthalmitis caused by virulent organisms (e.g., *Staphylococcus aureus*, streptococci, *Bacillus* species) also suffered from persistent retinal detachment; none of the patients retained postoperative visual acuity better than 3/200, and four (50%) lost light perception. Likewise, patients infected with fungal infection often have poor outcomes if the condition is not treated promptly and aggressively [32]. These mentioned findings emphasize the important fact that any case of infectious postoperative endophthalmitis is potentially devastating.

2.2.2. Open globe injuries with intraocular foreign bodies (IOFB)

2.2.2.1. Epidemiology and socioeconomic aspects

Open globe injuries with intraocular foreign bodies (IOFBs) are not only of special interest because of the needed ophthalmological treatment, but they are of fundamental importance because of their social and economic impact. Data of the World Health Organization (WHO) show that 55 million people annually are affected by eye injuries, 750000 of them need ophthalmological treatment, in 200000 cases open globe injuries are asserted. Other data from WHO show that yearly 1.6 million people worldwide go blind following eye injuries and at last 19 million incur unilateral blindness or severe vision loss [40; 41]. Ocular injuries are often accompanied by severe vision loss or blindness in the employable population and data range between 4 % in USA and 5 % / year in developing countries [40; 41]. Severe visual loss may be associated with the original injury, secondary endophthalmitis, rhegmatogenous retinal detachment (RD) or a variety of long-term complications including glaucoma, cataract, inflammation or foreign body toxicity [42]. Traumatic endophthalmitis and retinal detachment have a tendency towards to progress rapidly resulting in severe visual loss [43; 44]. Endophthalmitis has been reported in 2–30% of open-globe injuries with retained IOFBs [45; 46] and IOFBs have been estimated to occur in 10–41% of open-globe injuries [47; 43]. In the United Kingdom, Imrie et al. conducted an epidemiological study which showed that the incidence of open globe eye injuries with IOFBs is around 0,16 / 100000 of the population [48]. Other epidemiological studies based on data from the Eye Injury Register of the United States (USEIR) but also from Hungary (HEIR), showed that especially young male individuals under 30 years are exposed to a higher risk of sustaining such severe eye injuries. Here the data on all types of serious ocular trauma with IOFB’s reached from 54 % in Hungary to 60% in the USA [49]. Posterior segment IOFBs constitute the majority of IOFBs.

In the majority of cases, patients refer to their own home as location of the accident. But also other conditions could lead to a significant increase of open globe injuries with IOFBs. During the last decade, military operations such as in Iraq have highlighted features of combat ocular trauma, including open-globe, blast injuries and ocular adnexal lacerations. The extreme severity of open-globe injuries leads to high rates of primary enucleation and retained intraocular foreign bodies [50]. In summary, major risk factors for ocular injuries include age, gender, socioeconomic status and lifestyle. The site where the injury occurs is also related to a risk situation. Available information indicates a very significant impact of eye injuries in terms of medical care, needs for vocational rehabilitation and high socioeconomic costs. After sustaining a serious eye injury, the first question patients usually ask is whether they will lose some or all of their vision. Usually, prognoses are based on the personal experience of the physicians – and can be very accurate – but in cases where best estimates are incorrect, patients can be emotionally or psychologically devastated when they lose vision in one or both eyes. The advances consisting of, for example, in ophthalmological surgery with perfect vitrectomy techniques, application of retinectomy, using of laser and different tamponade devices, promise hope and better results in the treatment of these severe eye injuries [51; 52]. But long term results remain grave and, depending on the type of injury, they have a different or even worse prognosis.

2.2.2.2. Classification

Professional associations, such as the International Society of Ocular Trauma and the United States Eye Injury Registry have been formed to promote research on ocular injuries and disseminate their results. A standardized method to describe eye injuries was the basic to start projects like the Hungarian Eye Injury Register (HEIR) or the World Eye Injury Registry (WEIR) [49]. Clinical trials cannot be planned in the field of ocular trauma, therefore a standardized terminology for eye injury has been developed based on the extensive research, on retrospective evaluation of clinical data, on the experience of ocular surgeons and on the review by international ophthalmic audiences. The University of Birmingham, Alabama – United States – developed a system to classify eye injuries and which is still used from by the USEIR (United States Eye Injury Register) as the fundamental basis for the classification of ocular trauma. The Birmingham Eye Trauma Terminology Scale (BETTS) satisfies all criteria by providing a clear definition for all injury types and placing each injury type within the framework of a comprehensive system (Figure 1). The key to BETTS' logic is to understand that all terms relate to the entire eyeball as the tissue of reference. Basically, BETTS divides all eye injuries into closed globe injuries and in open globe injuries. The open globe injuries are further divided into lacerations and rupture wounds of the eye wall. Lacerations are full- thickness wounds of the eyewall, caused by a sharp object. We talk about a penetrating injury if the hurting object causes only an entrance wound. As opposed to this, we describe ocular trauma as a perforating injury if we find entrance and exit wounds. Eye injuries with intraocular foreign bodies (IOFBs) are technically a penetrating injury, but grouped separately because of different clinical implications [53; 54; 55]. In these studies, the entry site was categorized based on the wound's most posterior extent as zone 1 for cornea, zone 2 for sclera up to 5 mm posterior to the corneoscleral limbus, and zone 3 for sclera more than 5 mm posterior to the limbus. IOFBs are classified according to their location (anterior segment, posterior segment), material characteristics (metallic, magnetic, wood, glass), size, mechanism of injury, setting (work-related, battlefield), and duration (acute, long-standing).

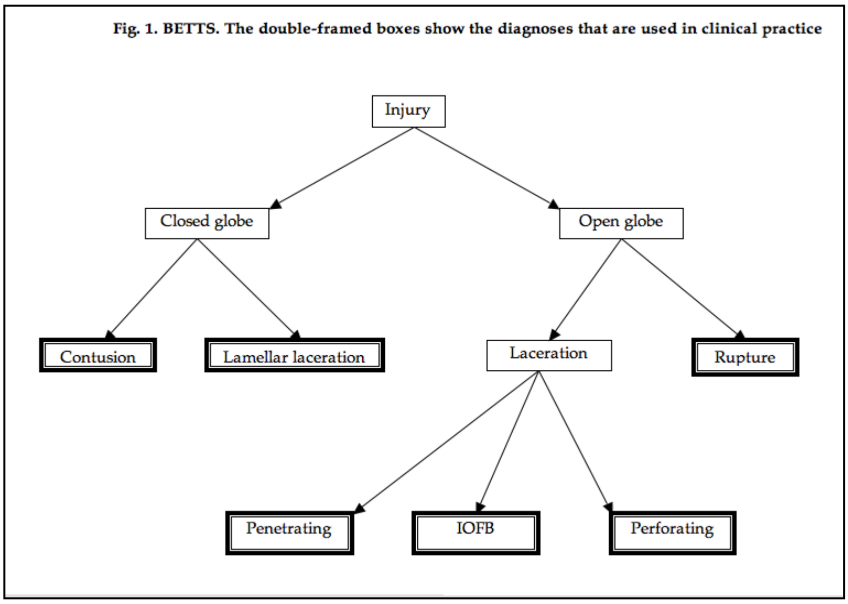


Figure 1. Classification of eye injuries in BETTS terminology ([http://isotonline.org)](http://isotonline.org)

Another method to describe ocular trauma is the application of the Ocular Trauma Score (OTS). This system was also developed by the above-mentioned research group in Birmingham, Alabama. The evaluation and calculation of the OTS score considers the amount of initial visual acuity, the presence of rupture of the eye, endophthalmitis, the presentation of penetrating wounds, detachment of the retina and the presence of relative afferent pupillary defect [56, 57]. By evaluating the clinical findings and calculating a number of points between 0 and 100, we can assign in OTS score between 1 and 5 to the eye trauma. However, open globe injuries with IOFBs are particularly significant because of the elevated risk for endophthalmitis and toxicity to the IOFB material, as well as the considerations specific to its surgical removal.

2.2.2.3. Diagnostics, management and guidelines for treatment

The examination primarily begins with an exact assessment of clinical history. Most open globe injuries with IOFBs are associated with a reported history of trauma to the eye. Patients in 1 series presented for examination on average 3.5 days after injury [46]. IOFBs are found in the anterior segment 21% to 38% of the time [46; 58]. Anterior chamber, iris surface, or intralenticular IOFBs are diagnosed easily in slitlamp examination. Iris, sulcus, and peripheral intralenticular IOFBs may be accompanied by iris defects, sometimes also iris sphincter tears, or sectoral or total cataract. Most posterior IOFBs are identified in the vitreous, but may also been localized in preretinal, subretinal or suprachoroidal space. If they are accompanied by vitreous hemorrhage and/or traumatic cataract, the visualization of IOFBs may be decreased or completely denied.

An accurate imaging examination before surgery is fundamental for the successful management of open globe injuries with or without IOFBs. B-scan ultrasonography is a proven, cost-effective imaging modality in the management of an open globe injury. Ultrasound characteristics are vitreous hemorrhage, vitreous floaters, retinal tear, retinal detachment, vitreous traction, vitreous debris, choroidal detachment, dislocated crystalline lens or intraocular lens (IOL), disrupted crystalline lens, intraocular foreign body (IOFB), intraocular air, irregular posterior globe contour, posterior vitreous detachment, vitreal membranes, and choroidal thickening [59]. Ultrasound is more user-dependent than CT (computed tomography), but can be up to 98% sensitive in detecting IOFBs in the appropriate clinical setting [42; 60]. However, CT has become the predominant imaging technique in the setting of ocular trauma. It is a standard protocol in the diagnostics of open globe injuries at many institutions. Another imaging instrument is the anterior segment optical coherence tomography, which has been used occasionally in the identification of anterior segment IOFBs, e.g. along the internal surface of the cornea, the angle and the iris. Otherwise, magnetic resonance imaging is not used for IOFBs despite its sensitivity because risk of metallic object movement and damage to the inner eye structures [61].

There are different protocols and considerations in the treatment of these severe eye injuries. A general recommendation is to perform primary surgery as soon as possible with wound closure and during the surgery the surgeon is invoked to clear anterior opacities if necessary (hyphema, cataract etc.). (Figure 2). In the case of foreign bodies it is the surgeon's decision whether the IOFB is removed immediately or delayed until the secondary surgery. Every acute treatment is followed by intensive postoperative care as necessary. This includes an option of systemic corticosteroids, other topical/systemic medications as needed and intravenous/intravitreal antibiotics [54].

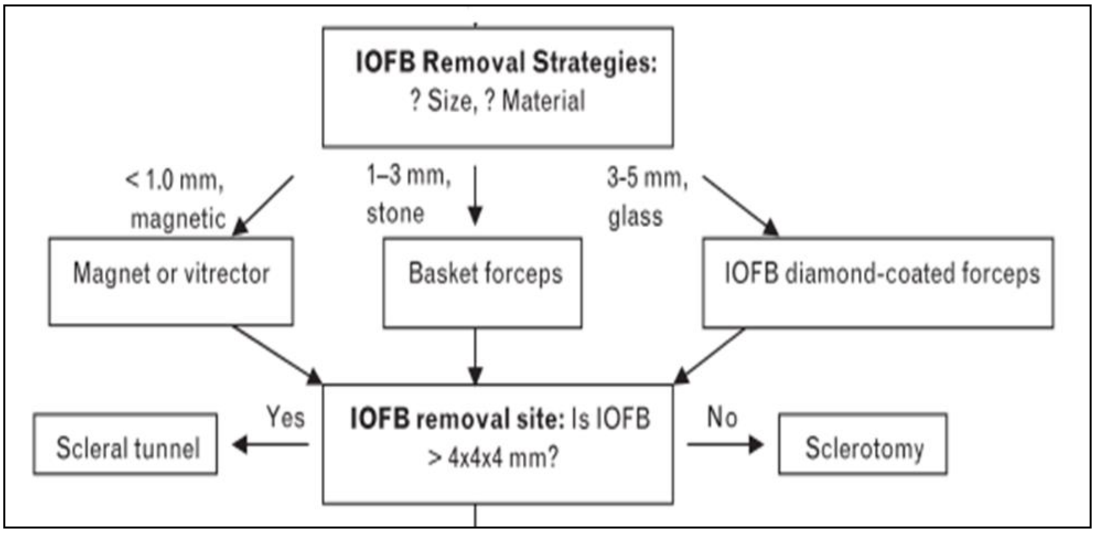


Figure 2: Strategies in management of eye injuries with IOFBs. (Yeh S, Colyer MH, Weichel ED (2008))

The follow-up of the patient is essential. The minimum recommended follow-up time is 6 months, whether or not oil is removed after pars plana vitrectomy. In general one-year follow-up is preferred, with scheduled visits in 1-3 months periods as preferred by the surgeon [62]. Documentation from admission to discharge after performed surgery has to be accurate and specific. The goal of an effective management is to reach optimal posttraumatic clinical outcomes and to avoid secondary posttraumatic proliferative vitreoretinopathy, which is a common complication following a variety of ocular injuries, and is associated with a poor visual outcome [63; 64]. Another redoubtable complication after surgery in open globe injuries is the emergence of endophthalmitis, especially after vitrectomy for removing od IOFBs.

2.2.3. Imaging techniques in POE and IOFB

2.2.3.1. Ultrasound

Ultrasound is an oscillating sound pressure wave with a frequency higher than the upper limit of the human hearing range (>20 KHz). Ocular ultrasonic imaging (sonography) has been used in clinical evaluation since 1956. Scientists have used high frequency sound waves to examine the eye and diagnose disorders when parts of the posterior segment of the eye were not visible, such as cataract, corneal opacities, blood in the vitreous fluid or other dysplastic malformations of the eye [65]. The typical frequencies used in diagnostic ophthalmic ultrasound are in the range of 8 to 20 MHz. Ultrasound biomicroscopy (UBM), based on 35- to 100-MHz transducers incorporated into a B-mode clinical scanner, provides high-resolution in vivo imaging of the anterior segment [66]. The most widely used scans in ocular sonography are the single dimensional A- scan and the 2 - dimensional B-scan [67]. B-scan echography uses a rapidly oscillating transducer to produce a "slice" through the globe in different sections. The echographic images can be viewed in real time. However, the B-scan is far superior to CT images in detecting and distinguishing between the different structures in the eye [68]. One of the most frequent indications for ocular echography is the examination of the retina in diabetic patients who have developed vitreous hemorrhage, but other important indications are the examination of intraocular tumors, intraocular inflammations, furthermore open globe injuries with or without intraocular foreign bodies. The methods most commonly used to detect intraocular foreign bodies are contact B scan ultrasonography and CT. In penetrating eye injuries ocular sonography is used to detect vitreous hemorrhages, integrity of the posterior eye wall, detachment of the retina and injuries of the lens and/or the lens bag [67]. Especially for open globe injuries with nonmetallic foreign bodies, such as organic, plastic, stone or glass IOFBs, or if this severe eye injury is associated with endophthalmitis, ultrasound examination (B scan) is essential to make an exact diagnosis, to plan the surgery and to follow the recovery postoperatively [69]. Careful examination is recommended in open globe injuries. UBM is also a valuable means in the evaluation of small, anteriorly located foreign bodies that may not be detectable by other methods [70].

In other intraocular inflammations such as toxocariosis, uveitis and in different types of endophthalmitis ultrasonography proved useful both for detecting involvement of the posterior segment and for monitoring the time course of the infection process [71]. Typical signs for inflammation in the posterior segment are detachment of vitreous body (vitreoschisis), inflammation cells and vitreous mass reflectivity, membranes, increased posterior eyewall thickness (PEWT) and detachment of the retina [67].

Ocular sonography is a painless, non-invasive technique and can be easily performed in the clinic, at the patient's bedside, or in the operating room.

2.2.3.2. Computed Tomography (CT)

X-ray computed tomography (CT) is a technology that uses computer-processed X-rays to produce tomographic images (virtual 'slices') of specific areas of a scanned object, allowing the user to see inside the object without cutting. X-ray CT is the most common form of CT in medicine. The term computed tomography alone is often used to refer to X-ray CT, although other types exist (such as positron emission tomography [PET] and single-photon emission computed tomography [SPECT]). The advantage compared to traditional medical radiography is the fact that CT completely eliminates the superimposition of images of structures outside the area of interest. CT imaging distinguishes up to 4000 grey shades. To measure the radiodensity we use the Hounsfield Unit (HU) scale. Basically we differentiate between axial and helical (also known as spiral) CT scanning. For ophthalmological imaging both methods are used and their cross-sectional images are analyzed for diagnostics and therapeutic purposes. Helical CT is a computed tomography technology involving movement in a helical pattern for the purpose of increasing resolution. The most commonly used images are in the axial or coronal and sagittal plane. This three dimensional imaging allows to produce also volumetric data. Furthermore, in high resolution CT (HRCT) differences between tissues that differ in physical density by less than 1% can be distinguished. Therefore, HRCT became therefore very important in the diagnostic of intraocular tumors, intraocular calcifications intraocular foreign bodies [72;73;74;67]. Orbital pathologies such as inflammations and tumors often present a diagnostic challenge for ophthalmologists. Native computed tomography does not guarantee optimal images, therefore a supplement with contrast agents (iodinated contrast media) can improve the quality of CT and also enables one to perform a dynamic imaging of the eye and orbit (CT angiography). Many authors describe the accuracy of CT imaging in ophthalmology [75; 76; 77]. Modern spiral CT has a very high sensitivity for detecting small intraocular foreign bodies (metallic and nonmetallic) up to 100% (confidence interval, 95%-100%; range, 0.88-1.00) [75; 78]. With the application of different collimations we can optimize the CT imaging by reducing examination time and radiation exposure. CT examination is an essential procedure for the diagnosis of open globe eye injuries with intraocular foreign bodies and fundamental for planning surgical treatment.

In hepatology, the manual tracing of the liver boundary on individual CT images is the standard technique for the calculation of liver volume. This is of high interest in the follow-up after extensive liver resections to estimate the postoperative results. Many published studies have been conducted to assess the accuracy of use of commercially available interactive volumetry-assist software in comparison with manual volumetry [79, 80; 81; 82; 83] and showed the high precision and reliability of this imaging method with a deviation of 0.05- 0,1 mm^3 [84]. Today, CT volumetry is applied in many branches of human medicine such as hepatology, neurology [85] and pulmonology [86], and it is used for the measurement and estimation of tumor size, bleedings, infarct areas and / or volume before and after surgical treatments. However, previously CT volumetry was not applied in clinical ophthalmology.

Computed tomography uses a „window” for the target tissue (measured in Hounsfield unity) to estimate the position and localisation. This attitude otherwise is a source for artefacts, especially for the localisation ocular foreign bodies. In some cases the imaging of the limit between choroid and sclera is not very clear, so that the radiologist may not be able to verify the exact position of the IOFB.

Three-dimensional reconstruction with high quality marginal sharpness and volume calculation may help the radiologist to better estimate the localisation and morphology of IOFBs, even if they are intra- or extraocular.

2.2.3.3. Optical coherence tomography (OCT)

Optical coherence tomography (OCT) has revolutionized the understanding and treatment of retinal diseases. As a non-invasive examination method similar to MRI, OCT produces cross-sectional images with high resolution using a light source [87; 88]. OCT is an echo technique and thus also similar to ultrasound imaging. Optical coherence tomography is based on low-coherence interferometry, typically employing near-infrared light. The use of relatively long wavelength light enables it to penetrate into the scattering medium. In 2002, the 3th generation TD- OCT (time domain optical coherence tomography) was widely introduced in daily clinical practice. In the following years, the development of spectral domain optical coherence tomography (SD-OCT) improved the quality and accuracy of the examination of retinal and choroidal structures. SD-OCT simultaneously measures multiple wavelengths of reflected light across a spectrum, as a consequence it is 100 times faster than TD-OCT and acquires 75,000 A-scans per second (Figure 3).

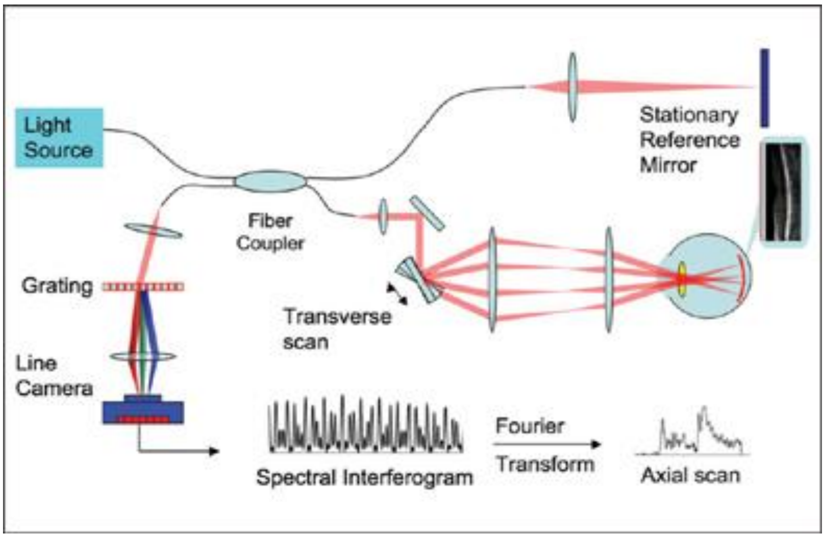


Figure 3: Schematic drawing of the principle of Spectral domain OCT. Light in an OCT system is broken into two arms — a sample arm (containing the item of interest) and a reference arm (usually a mirror). In SD-OCT it is essential to have a dispersive element to extract spectral information by distributing different optical frequencies onto a detector stripe (picture from www.ophthalmologymanagement.com/articleviewer.aspx).

The higher acquisition speed of SD-OCT minimizes motion artefacts and allows a higher resolution of retinal structures [89], thus providing more extensive morphological details [90]. Depending on the properties of the light source (superluminescent diodes, ultrashort pulsed lasers and supercontinuum lasers), OCT has achieved 3-5 micrometer resolution. The different layers of the retina and also of the choroid are easily distinguished by their optical reflectivity. In recent studies, SD-OCT technology has shown to have a high accuracy and also reproducibility in the imaging of retinal structures, retinal nerve fiber layer (RNFL), choroidal and corneal thickness measurements [91; 92; 93; 94; 95]. But with increasing depth into tissue, echoes are more difficult to discern from each other. Recent developments in OCT hardware, such as the enhanced depth imaging (EDI) technology [96] or recently the technologies from Swept Source OCT allow to reach optimal imaging from deeper structures. [97, 98]. Other correction software, such as adaptive compensation [99], have been reported to significantly improve the visibility of the lamina cribrosa (LC) without compromising acquisition time. This algorithm provided significant improvement by eliminating noise overamplification at great depth and improving the visibility of the deeper retinal structures, the choroid, and the posterior lamina cribrosa. Basically, the EDI-OCT modality places the objective lens of the SD-OCT closer to the eye, such that the light backscattered from the choroid is closer to the zero-delay and sensitivity is thereby enhanced. Therefore, this modality produces better imaging of the choroid. Many authors using enhanced depth imaging (EDI)-OCT reported satisfactory examination options and measurements of choroidal pathologies which promise choroidal OCT imaging to become a standard diagnostic procedure [100; 98].

In recent years, many authors have demonstrated in the last years the accuracy and reliability of spectral domain optical coherence tomography [90; 91; 92; 94; 101]. The Spectralis® OCT system is one of the numerous commercially available SD-OCT instruments [91; 94] and the first one capable of performing enhanced depth imaging (EDI). This technology allows to accurately examine the choroid and deeper structures of the retina. Margolis et al. measured the choroidal thickness with SD-OCT in 54 patients [96]. The values in this study (287 ± 76 µm) were similar to the values of histopathological examinations (average choroidal thickness 0,22 µm) [102]. Furthermore, assessments of central corneal thickness showed that SD-OCT is also an examination method with high precision [95]. Other recent studies showed that SD-OCT has a high accuracy and reproducibility in ONH and RNFL measurements in glaucoma. Other authors have also demonstrated also excellent reproducibility of the macular ganglion cell-layer plus inner plexiform–layer (GCL+IPL) thickness in glaucoma patients [103]. The thickness values of the retina measured by SD-OCT are influenced by the axial length [104]. Therefore, caution is recommended when comparing the measured values of short and long eyes with the normative database of the instrument.

3. Aims

3.1 Evaluation of data on endophthalmitis in Hungary

To collect and analyse data related to the current incidence and treatment of POE in Hungary

3.2 Ultrasound examination in POE

To evaluate the ultrasonographic features in patients with POE following cataract surgery

3.3 SD-OCT examination in patients after successful management of acute POE

To analyze the retinal and choroidal microstructure imaged by SD-OCT in patients after PPV due to post cataract endophthalmitis.

To study the correlation between central retinal thickness and choroidal thickness in eyes after post cataract endophthalmitis.

3.4 Clinical outcomes (prognostic factors) and imaging evaluation in patients with IOFB

To retrospectively analyse clinical features as well as the visual results of open globe eye injuries with IOFB.

To determine the prognostic factors after the removal of retained intraocular foreign bodies.

3.5 Accuracy of CT volumetry for measurement of IOFB

To evaluate the three dimensional reconstruction of CT imaging volume of intraocular foreign bodies (IOFB) using CT volumetry as a prognostic factor for clinical outcomes in open globe injuries.

4. Materials and methods

4.1 Evaluation of data on endophthalmitis in Hungary

We retrospectively collected data on 2678 patients with endophthalmitis from the database of the National Health Insurance Fund in Hungary covering the 8-year period between 1st of January 2000 and 31th of December 2007. Based on of the diagnosis (BNO - Betegségek Nemzetközi Osztályozása) and procedure codes (OENO - Orvosi Eljárások Nemzetközi Osztályozása) of the documented cases, we analysed the type of endophthalmitis, registered with different codes (H4400 purulent endophthalmitis; H4410 other endophthalmitis; H4411 endogen uveitis; H4419 other endophthalmitis without specification; H4510 endophthalmitis with other pathologies) and the nature of previous surgery and vitrectomy as a treatment for endophthalmitis. The classification of endophthalmitis in the mentioned database did not coincide with the ICD (International Statistical Classification of Diseases and Related Health Problems) classification. We compared the registered data on vitrectomy with the effective performed and reported surgical approaches to treat the endophthalmitis. Comparisons between these 2 groups were made using Student t tests and between multiple groups using analysis of variance ANOVA. (Statsoft® Statistica 8.0, confidence $p>0.05$).

4.2 Ultrasound examination in POE

At the Department of Ophthalmology of Semmelweis University, Budapest, Hungary, a retrospective analysis of data and ultrasound findings of 81 patients with endophthalmitis following cataract surgery was conducted during a 6 year period from 1st of January 2000 and 31th of December 2005. Patients came from other ophthalmological departments and were referred to the Department of Ophthalmology of the Semmelweis University as tertiary health care center. We excluded cases of endogenous endophthalmitis or with endophthalmitis after ocular trauma. In the study period, 86 patients (average age 70.39 years ± 14,9 SD) were treated at the above mentioned Department of Ophthalmology because of the onset of this inflammation, 81 of them referred ultrasonographic data. We evaluated the type of cataract surgery, time of onset of endophthalmitis, and different ultrasonographic findings such as opacities in vitreous cavity, membrane formations, detachment of posterior hyaloid, detachment of the choroid and /or of the retina, formation of abscess or granulomas, swelling of optic nerve and thickness of the posterior eye wall (PEWT). All ultrasonographic examinations were performed using the Alcon „Ultrascan" (B-mode, Alcon Inc., USA.) with a 10 MHz probe. Most examinations were performed by a single examiner (88%), settings and examination methods except the decibel (db) gain were identical. Examinations were systematically focused on echo sources in vitreous cavity, retrohyaloid space and on PEWT. Statistical evaluation was performed using nonparametric Mann-Whitney-Test (Statsoft® Statistica 6.0, confidence $p>0.05$).

4.3 SD-OCT examination in patients after successful management of POE

Between 1st of July 2012 and 31th of January 2013, a cross sectional, observational study was carried out at the Department of Ophthalmology, Semmelweis University, Budapest, Hungary. The enrolled patients had undergone bilateral cataract surgery and PCL implantation with postoperative endophthalmitis in one eye. Our department provides regional tertiary care for endophthalmitis and therefore the majority of post cataract endophthalmitis cases are referrals from surgical centers performing the surgeries. The study was approved by the Ethical Committee of Semmelweis University, Budapest and the Hungarian Human Subjects Research Committee (750/PI/2012. 49765/2012/EKU). All patients provided written informed consent. The study was conducted according to the tenets of the Declaration of Helsinki. Patient charts were evaluated retrospectively where pars plana vitrectomy was performed in the period between 2008 and 2012 due to severe acute endophthalmitis following cataract surgery and obtained clear optic media after recovery. Twenty-five patients were invited to participate in the study, seventeen patients agreed to visit our department and give consent. The age range was 56 to 89 years (69.5 ± 7.8 years, median 68 years), 7 patients were female. All patients underwent phacoemulsification and posterior chamber intraocular lens implantation in both eyes. The patients developed postoperative endophthalmitis between 2008 and 2012. The acute onset postoperative endophthalmitis cases – all within 8 days after successful cataract surgery – were managed by pars plana vitrectomy (with complete detachment of the posterior hyaloid confirmed by intraoperative triamcinolone staining) performed within 24 hours of the outbreak. Within 4 weeks after vitrectomy the optical media of all patients cleared up. The average time for the SD-OCT assessment performed after the vitrectomy was 48 ± 34 months. Only patients with artificial intraocular lens bilaterally were enrolled to reach similar postoperative conditions. Exclusion criteria included known ocular diseases such as glaucoma, diabetic retinopathy or exudative age-related macular degeneration (AREDS 3 classification or higher). Patients with high myopia, over minus 6 diopters or with an axial length over 26 mm were also excluded from the study. Two patients were myopic with an axial length under 26 mm. First, the refractive power was determined with an autorefractor keratometer and BCVA (best corrected visual acuity) was assessed by using ETDRS charts in both eyes of all patients. Then slit-lamp examination of the anterior segment was performed followed by fundoscopic examination after pupillary dilation. SD-OCT examinations were performed in all eyes by a single experienced examiner (EV) using Spectralis (Heidelberg Engineering, Heidelberg, Germany) SD-OCT, which provides up to 40000 A-scans per second with 7 μm depth resolution in tissues and 14 μm transversal resolution of images of ocular microstructures. Correct posture, head position, focus on the video imaging and centralization of the scan area were carefully monitored along with optimal scan settings. After each examination, the best image was assessed. Using the standard software of Spectralis OCT (Spectralis software v.5.1.1.0; Eye Explorer Software 1.6.1.0, Heidelberg Engineering), we assessed the central and peripheral macular thickness and macular volume. The presence of epiretinal membrane was recorded in both groups along with the presence of severe traction (i.e. traction causing disappearance of the foveal contour). Peripapillary retinal nerve fiber layer (RNFL) thickness measurements were performed using a 12-degree diameter circular scan pattern. The average RNFL thickness value provided by the software was used for further analyses. For the measurement of choroidal thickness patients underwent enhanced depth imaging spectral-domain optical coherence tomography which was obtained by positioning the device close to the eye and employing the automatic EDI mode of the device. A horizontal linear section comprising 50 averaged scans was obtained of each macula within a 20° x 20° area. The OCT protocol was performed focusing on the fovea. Choroidal thickness was measured in 7 manually selected points in the macula by using a caliper scale provided by the software of the SD-OCT device: one in the fovea, two points located temporally and nasally from the fovea in the horizontal meridian at a distance of 2000 μm, and 4 points located superior and inferior to the temporal and nasal horizontal measurement locations, also at a distance of 2000 μm (Figure 4). Choroidal thickness was measured by the caliper tool from the outer border of the retinal pigment epithelium to the inner scleral border (Figure 5). During a single examination, operators can easily switch between 'standard' and 'EDI-OCT' mode. All measurements were conducted by a second independent examiner (OM) who was masked to the patient and eye data that were analyzed.

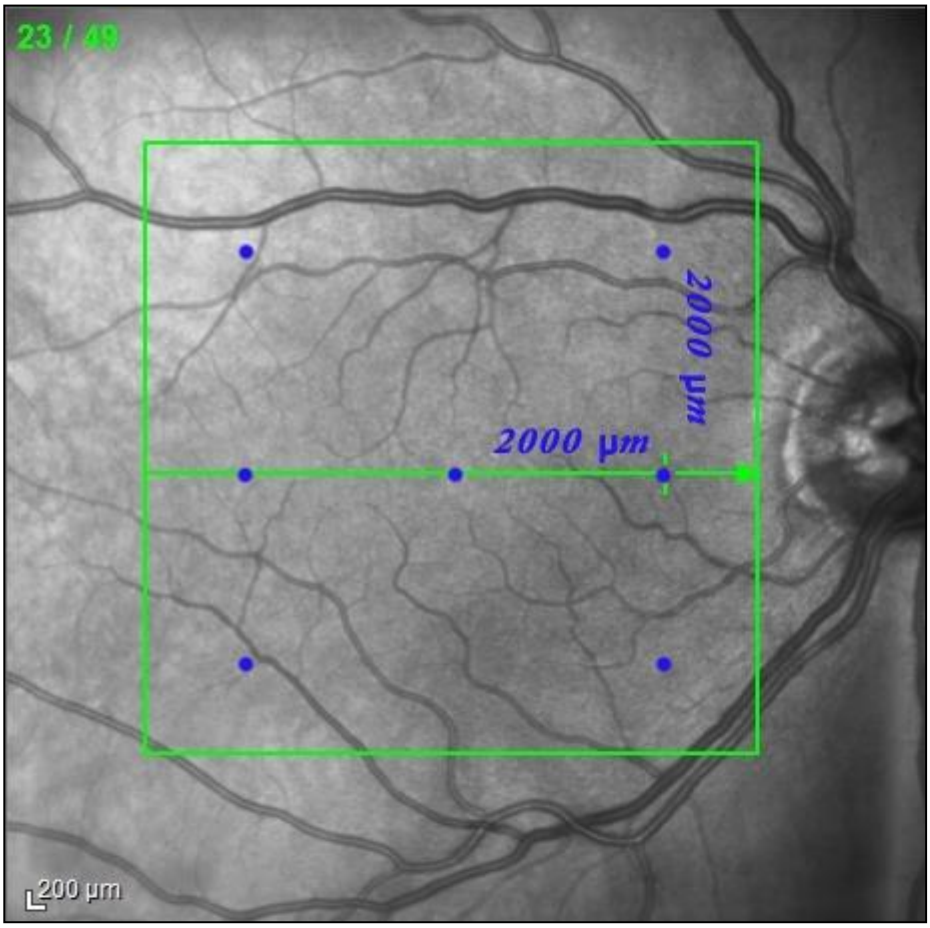


Figure 4: The blue dots on the infrared fundus image denote the measurement points used in the study. Each measurement point has a distance of 2000 um on the central horizontal and two vertical axes (Maneschg OA et al.; BMC Ophthalmol 2014, Jun 2;14(1):76)

Pairwise comparisons were made between the post-endophthalmitis eye (study eye) and the fellow healthy eye (control eye). The statistical analyses were performed using the Statistica 8.0 software (Statsoft Inc., Tulsa, USA). Data were expressed as mean values ± standard deviation. Wilcoxon nonparametric test was used for the comparison of thickness data between the study and control eyes. The occurrence of epiretinal membranes was compared by Fisher exact test. Spearman rank order correlation test was performed between central retinal thickness and subfoveal choroidal thickness. The level of significance was set at $p < 0.05$.

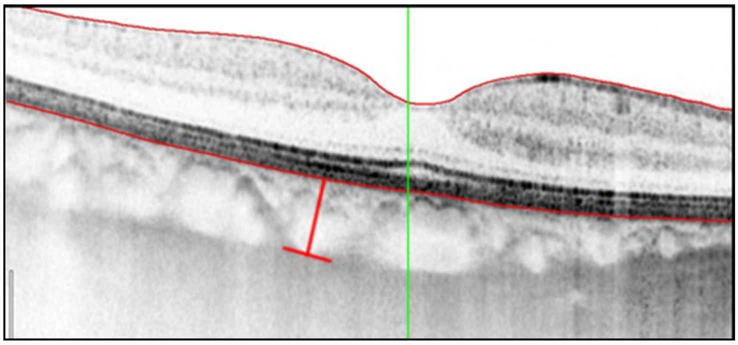


Figure 5: SD-OCT image in EDI mode in an eye after postoperative endophthalmitis. Choroidal thickness is measured between the outer border of the retinal pigment epithelium and the inner scleral border using the caliper tool of the software (red line). (Maneschg OA et al.; BMC Ophthalmol 2014, Jun 2;14(1):76)

4.4 Clinical outcomes (prognostic factors) and imaging evaluation in patients with IOFB.

At the Department of Ophthalmology of Semmelweis University Budapest, Hungary, we conducted a non-randomised, non-comparative retrospective analysis of records of 31 patients with intraocular foreign bodies treated by pars plana vitrectomy and other conventional surgical techniques during a 3-year period between January 2006 and December 2008. During the time of the study, we evaluated the age of the patients, gender, the size of the IOFBs, the pre- and postoperative best corrected visual acuity (BCVA), the time between injury and performed removal of the IOFBs, the type of surgery, the follow-up and the clinical outcome. We classified the ocular injury using the OTS classification for ocular injuries (United States Eye Injury Registry [USEIR]). Inclusion criteria were open globe injuries with one or more IOFBs, caused by laceration with sharp objects. We excluded contusions, perforations and eye rupture due to blunt eye trauma. Based on the patients' documentation, we evaluated the BCVA in different time frames after surgery. BCVA as standard procedure was evaluated on the 1st day postoperatively, furthermore on week 1, month 1, month 3 and month 6 or more after surgery. We noted that not all patients attended the examinations on a regular basis; especially long time after surgery the checkups became seldom. Because of the retrospective nature of this study, we noted that visual acuity was not documented in a standardized way. In some cases visual acuity was examined with ETDRS charts, in other cases, with methods that are well-established in our department, such as using different optotypes in 1 or 5 m distance. We calculated the visual acuity in decimal counts using the algorithms of Bach and Kommerell [104].

Initial visual factor		**Raw Points**
1) Initial visual acuity		no light perception = 60
		Light perception to HM * = 70
		1/200 to 19/200 = 80
		20/200 to 20/50 = 90
		≥ 20/40 =100
2) Globe rupture		-23
3) Endophthalmitis		-17
4) Perforating injury		-14
5) Retinal detachment		-11
6) Afferent pupillary defect		-10
** HM = Hand movements*		

Table 1: Computational method for deriving the OTS score (Kuhn et al. 1996)

We used the „Ocular Trauma Score" Scale (OTS). The calculation of the OTS grade considers the visual acuity at the time of admission, the evidence of eye rupture, endophthalmitis, the presentation of penetrating wounds, detachment of the retina and the presence of relative afferent pupillary defect (RAPD). By evaluating the severity of these clinical findings we can calculate an OTS „raw score” between 0 and 100 (Table 1), and consecutively we can deduce an OTS score between 1 and 5. (Table 2)

Correlation between "raw score" and OTS score	
raw score	**OTS score**
0-44	1
45-65	2
66-80	3
81-91	4
92-100	5

Table 2: Calculation of Ocular Trauma Score (Kuhn et al. 1996)

The main point of interest was to evaluate the differences in the clinical outcome between eye injuries of lower and of higher OTS score. We also evaluated the correlation between the referred point in time of the eye injury and the performed ocular surgery and the BCVA at this mentioned time. Furthermore we evaluated the effect of the size of IOFBs on the final visual acuity. We manually measured the size of IOFBs with calipers. For linear calculation we converted the decimal values in logMAR values (Logarithm of the Minimum Angle of Resolution). For the visual acuity of „hand movements” we used the logMAR value of 2, for BCVA of only light perception (decimal visual acuity 0,008) we used the value logMAR 2.1 [104]. For statistical evaluation we used the non parametric Student T-test (Statistica 8.0 Statsoft Inc, Tulsa, OK, USA), $p<0.05$ was considered significant.

4.5 Accuracy of CT volumetry for measurement of IOFB

We compared the volume of 11 IOFBs over 5 mm^3 based on CT volumetry, with the real size also determined by in-vitro volume measurement. For volume calculation we used the following software: Philips Extended Brilliance Workspace, Brilliance 3.5 (Koninklijke Philips Electronics N.V.). We compared pairwise 11 intraocular foreign bodies with a volumetric calculated volume over 5 mm^3 by measuring them with the water displacement. We excluded smaller IOFB’s because of the possible inaccuracy in manual measurement. We used micropipettes P100 (Gilson Inc. Middleton, USA) with pipette tips of 0.5 – 20µl (e.p. TIPS, Eppendorf AG, Hamburg). Furthermore we used current dropping glasses (4 mm gouge, Lab-Laborfachhandel®, München) and inserted 200 µl water volume. We marked the water level, inserted the foreign body in the dropping glass and marked the new water level on the outer glass-site. Subsequently we removed the water volume to the point of the first marked line and compared this volume with the calculated data from the volumetry software. For the pairwise statistical analyses we used the comparative Wilcoxon Test (Statistica 8.0, Stasoft, Tusla, USA), $p<0.05$ was considered significant.

For the correlation between visual outcome and IOFB size, we performed a retrospective evaluation of documented clinical data, medical history, visual acuity, complications, relation to size of IOFBs, and clinical outcomes of 33 patients (mean age 41.0 ± 13.5 years). All patients have been treated over a period of six years, between January 2005 and December 2010, at the Department of Ophthalmology, Semmelweis University, Budapest, due to open globe injuries with IOFB. We classified the eye injuries according to OTS. Using CT volumetry software, we calculated the exact size and position of IOFB.

We divided three groups based on the size of IOFB: group 1: 5-15 mm^3; group 2: 16-35 mm^3, group 3: >35 mm^3, and compared the groups to the final visual outcomes.

We compared the initial visual acuity with the postoperative BCVA. For statistical analysis, we converted the decimal values in logMAR values for visual acuity to obtain a linear correlation. We used the Student T-test and the Mann-Whitney-U-test to evaluate significant differences (Statistica 10.0, Stasoft Inc., Tusla, OK, USA).

5. Results

5.1 Evaluation of data on endophthalmitis in Hungary

Between 2000 and 2007, 1660 cases of endophthalmitis and 1010 endogenous uveitis cases were registered in Hungary. Most cases of endophthalmitis (266) were registered in 2001. In 2007 we registered a minimum of 165 cases. The calculated incidence of endophthalmitis in Hungary was 2.19 per 100,000 in 2000, which decreased to 1.65 per 100,000 population in 2007. There were some regional differences, with the highest incidence in the southeastern region (Dél Alföld; 13 cases / 100000 popul. / year) and the lowest incidence in the southwest (Dél Dunántúl; 3.6 cases / 100000 popul. / year). In the study period, altogether 501 cases of postoperative endophthalmitis were reported (Figure 6). The number of postoperative endophthalmitis cases decreased from 103 in 2000 to 40 in 2007. The incidence of endophthalmitis after open globe surgery was about 0.07%. In this 8-year period, cataract surgery was the most common cause of postoperative endophthalmitis (381 cases; 74%), followed by vitrectomy (90 cases; 17.9%), perforating keratoplasty (20 cases; 3.8%) and trabeculectomy (8 cases; 1.6%) (Figure 5). Based on this data we calculated the average incidence (0.067%) of postoperative endophthalmitis during this 8-years period (501 cases and 739923 open globe surgeries). The incidence of endophthalmitis following cataract surgery was estimated to be 0.058 %, and decreased over the study period (Figure 7).

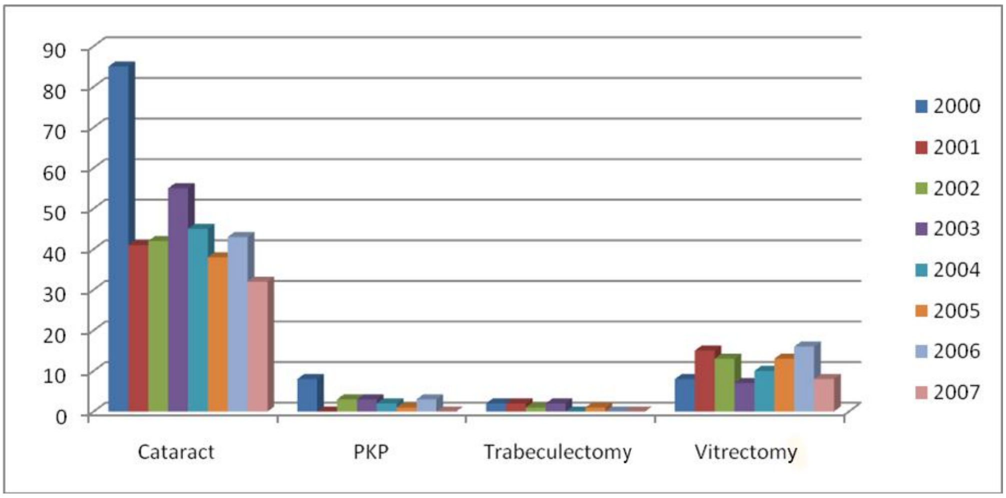


Figure 6: Incidence (cases) of postoperative endophthalmitis in Hungary from 2000-2007 (Németh J, Maneschg O, Kovács I: Szemészet 2011; 148: 42-4)

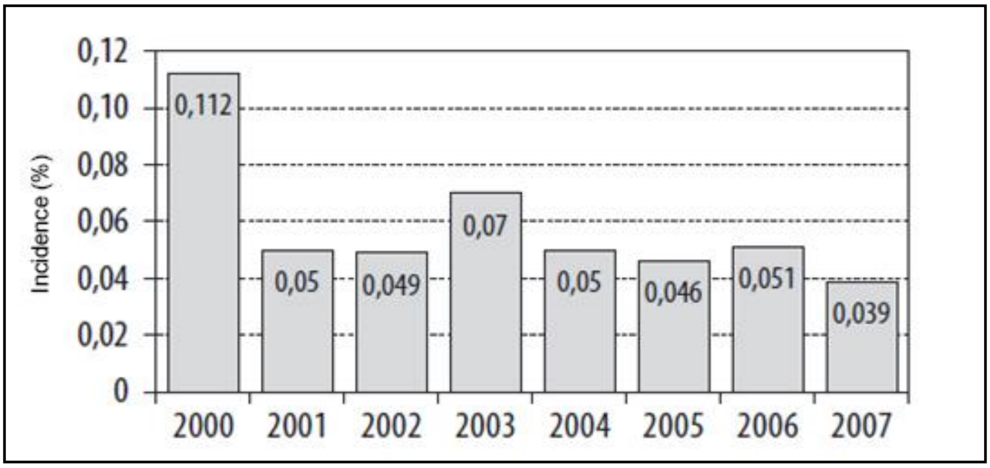


Figure 7: Incidence of endophthalmitis in Hungary following cataract surgery (Németh J, Maneschg O, Kovács I: Szemészet 2011; 148: 42-4)

As described above, today PPV is a standard procedure for the treatment of acute postoperative endophthalmitis. We noted that in 2000, PPV was performed in 71 % of these severe postoperative complications, and it increased in the following years (100% in 2007) (Figure 8). In the 8-year period, vitrectomy was performed as a treatment in 413 cases of postoperative endophthalmitis (in 82.4% of all the cases).

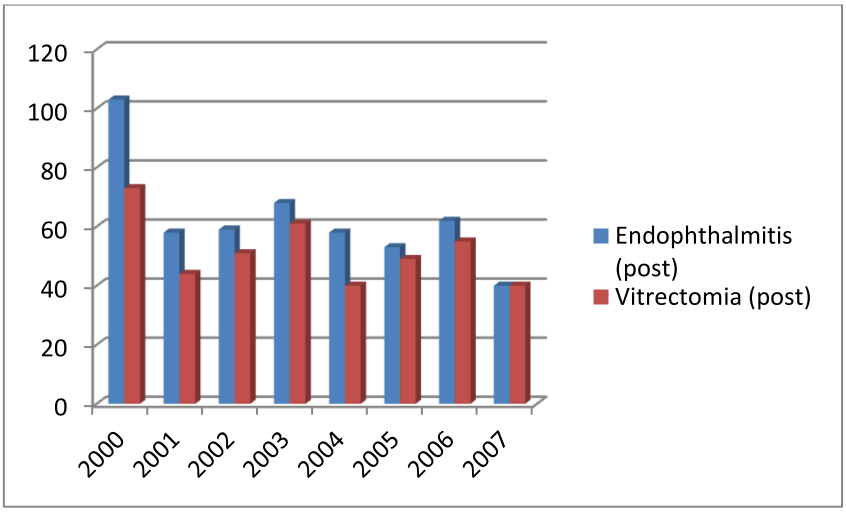
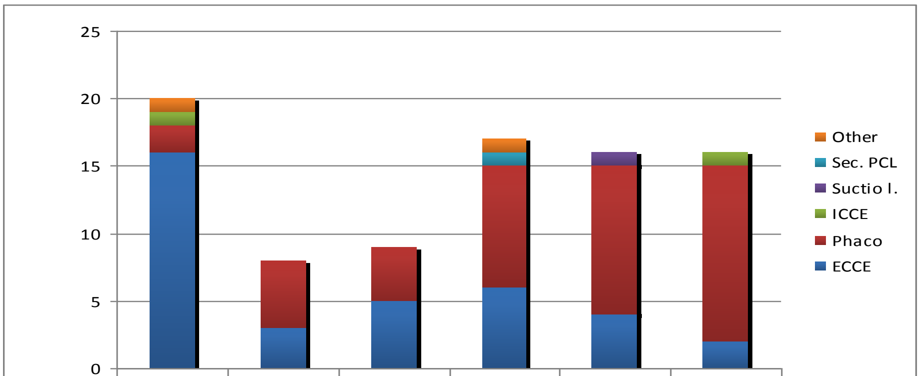


Figure 8. Correlation between postoperative endophthalmits and performed vitrectomy. Note the increase in the rate of vitrectomy from 71% in 2000 to 100 % in 2007 (Németh J, Maneschg O, Kovács I: Szemészet 2011; 148: 42-4).

5.2 Ultrasound examination in POE

At the Department of Ophthalmology of Semmelweis University, Budapest, during a study period of six years (January 2000 – December 2005), we examined data of 218 patients with endophthalmitis of different etiologies, 137 cases of them were POE, in 86 cases after cataract surgery. In the data reported, acute-onset POE (1-6 days after the cataract surgery) was described in 41 eyes (47.7%), a subacute POE (within 6 weeks) in 25 eyes (29%). Late- onset POE was described in 20 eyes (23.3%). In 51 % of the cases, endophthalmitis occurred following the phacoemulsification method, the remaining 49 % after other techniques such as ECCE or ICCE cataract extraction, implantation of secondary IOL, suctio lentis + IOL implantation, combined vitrectomy and phacoemulsification (Figure 9).



	2000	2001	2002	2003	2004	2005
Other	1	0	0	1	0	0
Sec. PCL	0	0	0	1	0	0
Suctio l.	0	0	0	0	1	0
ICCE	1	0	0	0	0	1
Phaco	2	5	4	9	11	13
ECCE	16	3	5	6	4	2

Figure 9: Type of cataract surgeries followed by postoperative endophthalmitis (POE) during a six-years period from 2000 to 2005: Sec. PCL: secondary posterior chamber lens implantation; Suctio l: suctio lentis; ICCE: intracapsular cataract extraction; ECCE: extracapsular lens extraction; Phaco: Phacoemulsification (Maneschg O, Csákány B, Németh J: Ophthalmologe 2009; 106: 1012-1015)

63 patients were sent for treatment to our department as a tertiary referral center by other institutions. During the study period, calculated incidence of POE (23 cases) after a total volume of 13803 cataract surgeries amounted to 0.16%.

Eighty-one patients have reported ultrasonographic data.

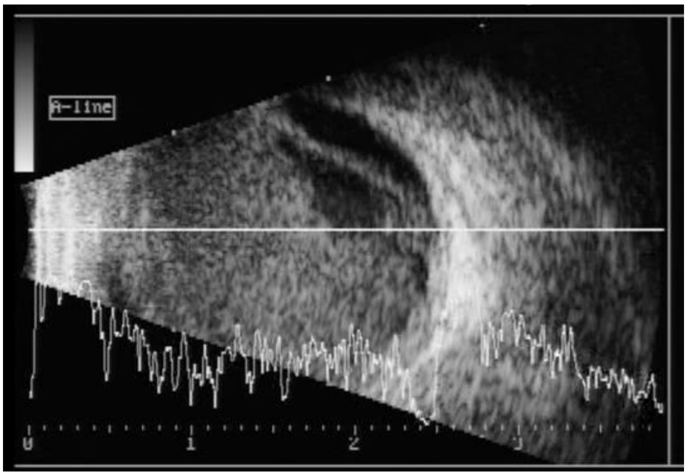


Figure 10: B-Scan of a 49-year old male patient with acute (3 days) endophthalmitis following cataract surgery. We observe a high reflectivity in vitreal cavity with lacunes and retinal/hyaloid detachment. (Maneschg O, Csákány B, Németh J: Ophthalmologe 2009; 106: 1012-1015).

Ultrasonographic findings such as membrane formation were detected in 23 eyes (28%); dense vitreous opacities (Figure 10) were detected in 9 eyes; detachment of the choroid was reported in 3 eyes and of the retina in 4 eyes.

	acute	sub-acute	late dev.	
Detach.ret.+ chor.	2	4	0	7,40%
Detach. ret.	2	2	0	4,94%
Detach.chor.	2	0	1	3,70%
Detach.post.vitreous	10	5	3	22,0%
Mobil.echo	15	12	2	35,80%
Membranes	12	5	6	28,40%
Tractiones	2	5	1	9,80%
Lacunes	3	7	5	18,50%
Mass – dense vitr.opac.	6	2	1	11%

Table 3: Ultrasonographic findings in POE after cataract surgery of 81 patients. Detach.ret.and chor.: Detachment of the retina and choroid, detach.post.vitreous: Detachment of the posterior hyaloid (vitreous). (Maneschg O, Csákány B, Németh J: Ophthalmologe 2009; 106: 1012-1015)

In 6 eyes both layers, choroid and retina together, were detached. Two findings of initial echography were associated with acute and subacute endophthalmitis: dense vitreous opacities and detachment of posterior hyaloid membrane (Table 3). Increased thickness of the posterior eye wall was reported in 73 cases (Figure 11).

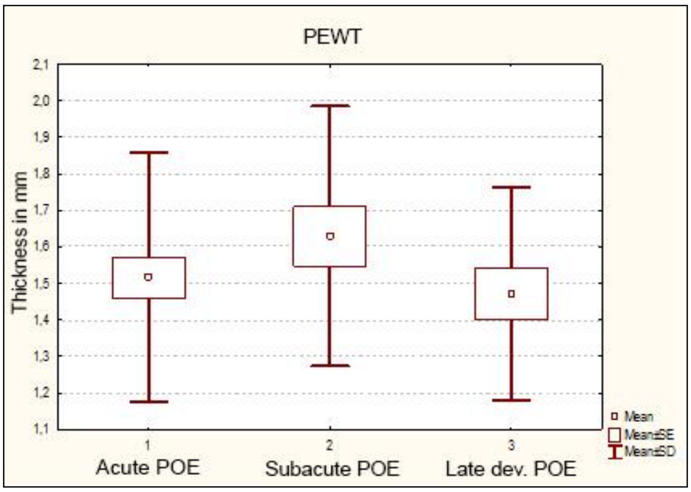


Figure 11: Posterior wall thickness (mean±SD) was calculated as 1.51±0.34 mm in acute and 1.62±0.35 mm in subacute cases and was compared with late developed cases (1.47±0.29 mm), but the difference was not statistically significant (p>0.05, Mann-Whitney non-parametric test) (Maneschg O, Csákány B, Németh J: Ophthalmologe 2009; 106: 1012-1015)

5.3 SD-OCT examination in patients after successful management of acute POE

The mean visual acuity of the patients before performing vitrectomy was 0.03, 11 of them had a visual acuity of HM (hand movement) and 2 subjects had only LP (light perception). The patients were treated intraoperatively and after vitrectomy with vancomycin/amikacin, ceftazidim and steroids for an average period of 8 days. Vitrectomy was performed in all cases without complication, there were no vitreous hemorrhages or retinal detachments during or after the surgeries. Microorganisms were isolated from eight specimens, with seven cases of *Staphylococcus spp*. among them. Mean postoperative BCVA was 63± 30 ETDRS letters in the study eye group and 75± 21 ETDRS letters in the control group (p = 0.1). Mean retinal thickness in the study eyes was 320.6 ± 28.83 µm and 318.4 ± 18.8 µm in the control eye group (p = 0.767) and there was no difference in thickness of the remaining eight macular regions, either. (Table 4).

Macular region	Endophthalmitis (study) eye in µm	Control (fellow) eye in µm	p value
superior near	303 ± 51.56	308.9 ± 40.69	**0.68**
superior far	358.6 ± 44.52	335.7 ± 46.08	**0.27**
nasal near	306.9 ± 37.63	314.3 ± 25.06	**0.68**
nasal far	359.3 ± 46.94	344.9 ± 54.5	**0.68**
inferior near	297.9 ± 57.85	295.3 ± 34.95	**0.61**
inferior far	348.6 ±43.45	335.9 ± 47.46	**0.2**
temporal near	279.4 ± 44.38	297.4 ± 50.14	**0.97**
temporal far	325.3 ± 49.2	331.5 ± 43.02	**0.91**
central (CRT)	306.7 ± 78.35	302 ± 82.17	**0.66**
Mean ± SD	320.6 ± 28.83	318.4 ± 18.8	**0.76**

Table 4. Retinal thickness changes in the different macular regions in the study groups (mean ± SD). CRT: central retinal thickness. (Maneschg OA et al.; BMC Ophthalmol 2014, Jun 2;14(1):76).

The endophthalmitis group showed a mean macular volume of 8.79 ± 0.92 μm^3 and 8.9 ± 0.91 μm^3 in the control eyes (p = 0.97). In the endophthalmitis study eye group, the mean RNFL thickness was 92.2 ± 15.1 µm, while it was 97.8 ± 18.4 µm in the control eye group, the difference was not significant (p = 0.31). In 4 cases of the endophthalmitis eyes, the software assessed peripapillary mean RNFL thickness being below normal or borderline, compared to 3 RNFL measurements in the control eyes. (Figure 12).

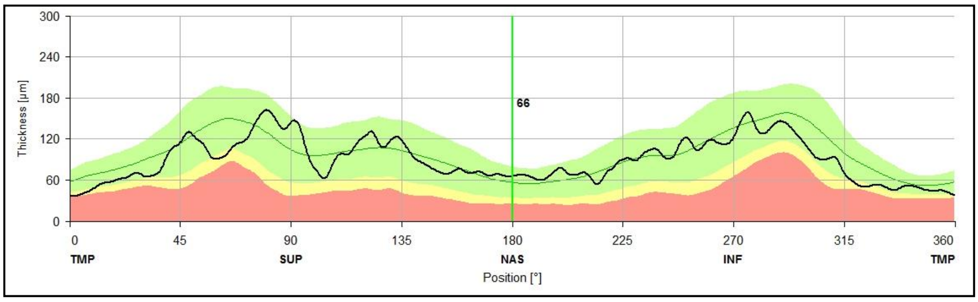


Figure 12: Measurement of the peripapillary nerve fiber layer thickness in an eye after post cataract endophthalmitis. Note that the thickness curve is running mostly within normal limits, except for the temporal and superotemporal regions (Maneschg OA et al.; BMC Ophthalmol 2014, Jun 2;14(1):76).

In six eyes of four patients, early stages of age-related macular degeneration (stage 1-2 AREDS classification) were detected with slight pigment alteration and drusen but no lesion activity. Another frequent clinical finding in the study group was the development of epiretinal membranes (7 cases vs. 3 cases in the fellow eyes, p = 0.13, Fisher exact test), all without severe traction.

Choroidal thickness in the central, temporal superior, temporal inferior, nasal superior and nasal central region was found significantly lower in the study eyes (p = 0.03, 0.007, 0.09, 0.02 and 0.049, respectively). In other regions, choroidal thickness was also decreased, but the difference was insignificant (p = 0.33, 0.36) (Figure 13).

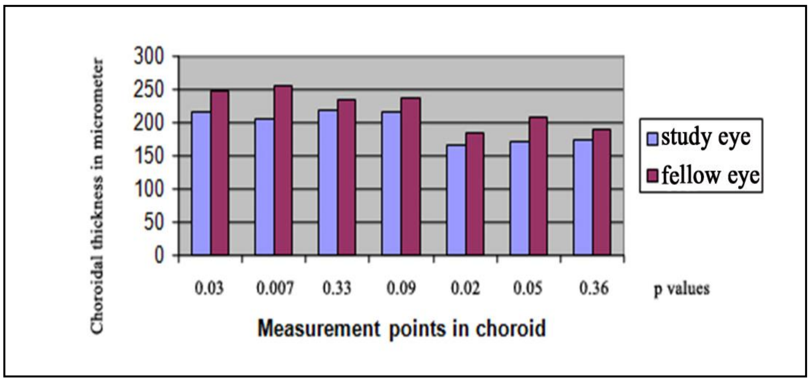


Figure 13: Choroidal thickness in the different measurement regions and mean choroidal thickness comparison between study eye and fellow eye. Significant changes of decreased thickness were found in the central, temporal superior, nasal superior and nasal macular areas in eyes after postoperative endophthalmitis (Maneschg OA et al.; BMC Ophthalmol 2014, Jun 2;14(1):76)

In the study eyes, mean choroidal thickness was significantly lower compared to the control eyes (195.14 ± 23.19 µm and 221.86 ± 28.47 µm, respectively, $p = 0.018$) (Figure 14). There was no significant correlation between central retinal thickness and choroidal thickness of the study and fellow eyes in the foveal region ($p > 0.05$) (Figure 15).

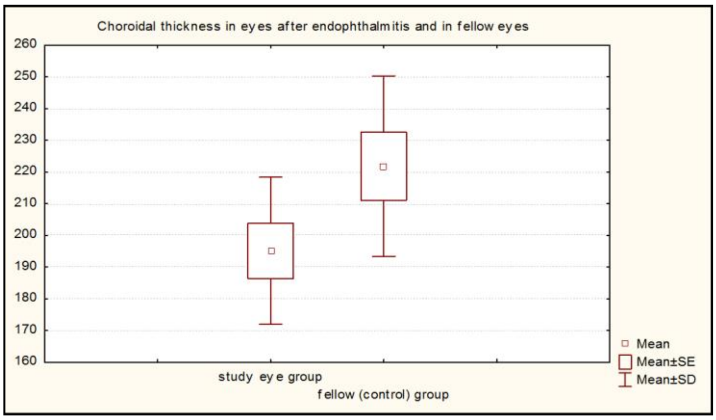


Figure 14: Compared to eyes after uncomplicated phacoemulsification (221.86 µm ± 28.47) mean choroidal thickness is significantly thinner in eyes after endophthalmitis (195.14 µm ± 23.19), (p = 0.018). (Maneschg OA et al.; BMC Ophthalmol 2014, Jun 2;14(1):76)

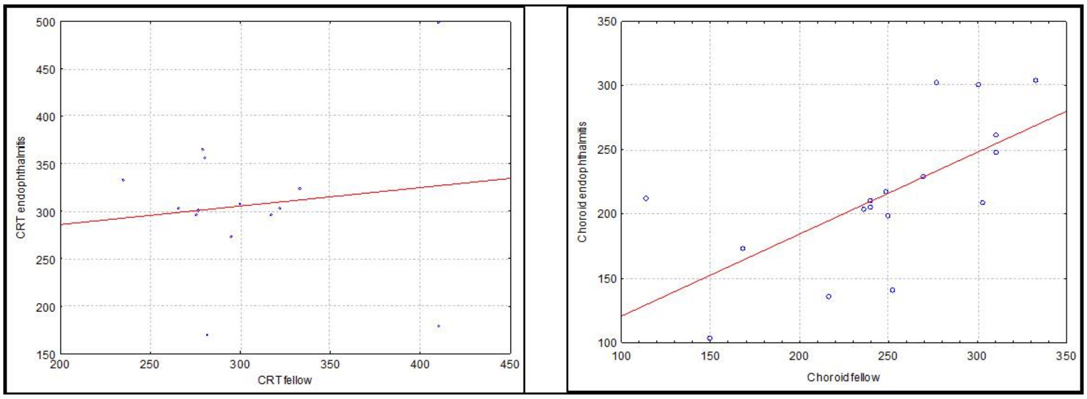


Figure 15: No correlation was observed between CRT and subfoveal choroidal thickness in the study and fellow eyes. (Spearman Rank Order Correlation, p > 0.05) (Maneschg OA et al.; BMC Ophthalmol 2014, Jun 2;14(1):76)

5.4 Clinical outcomes (prognostic factors) and imaging evaluation in patients with IOFB.

Almost all patients (96.8%) were male with a mean age of 32.29 years ± 13.38 SD. In most cases (55%), patients reported that the injury happened at home, in 32% the accident happened at work and in the other cases (12.9%) the site of the accident was not known. The most common causes were hammering on metal (58 %), explosion of pressure vessels (22.5%), use of grinders (16.1%) and in one case (3.2%) drilling of metal-concrete mixtures. In all 31 cases (patient group 1), an open globe injury with intraocular foreign bodies was diagnosed (Figure 16). In 27 cases, the IOFB was magnetic. A relative afferent pupillary defect was described in only one case. Preoperatively, we found 5 retinal detachments and 2 cases of endophthalmitis. At the time of surgery, initial vitreous hemorrhage was present in 17 patients (54.8%).

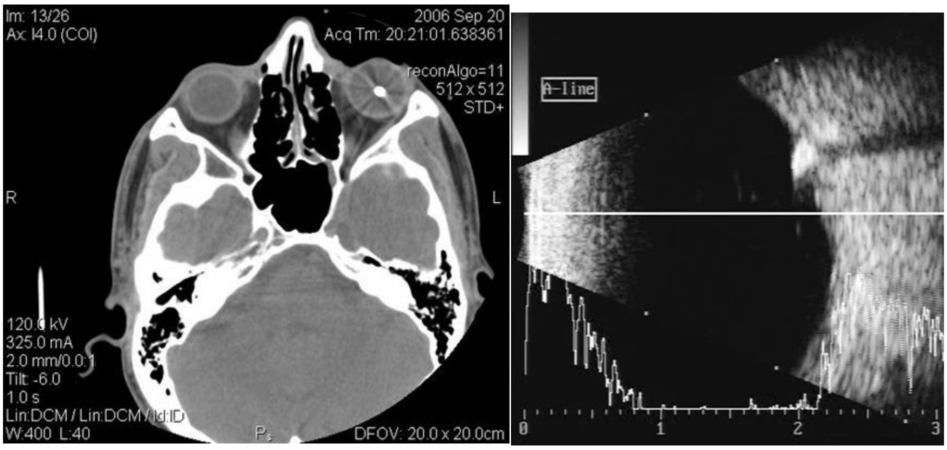


Figure 16: Imaging (CT and ultrasound) of a metallic IOFB in a left eye in a 41 years old male patient who suffered an accident while using of grinders. The patient did not wear safety glasses at the time of injury (Maneschg OA et al.; Klin Monatbl Augenhd. 2011 Sep; 228:801-7).

Based on the existing visual acuity in the recording and the clinical findings we determined an OTS - injury level for each patient. The average value according to the OTS scale was 2.45 ± 0.78 SD. In 30 eyes, the IOFBs could be removed during the first surgery. The average time between injury and surgery was 15.78 ± 23.45 SD hours for 27 patients (87.1%). In 3 cases, the intraocular foreign body (IOFB) was removed 7, 9, 14 days after the injury. In one case, the IOFB was removed in a second surgery 40 days after the injury. In 23 cases (74%) we performed pars plana vitrectomy, for 8 patients we performed only anterior segment surgery, in 21 cases the lens was also removed. In every case computed tomography was performed preoperatively, in 20 cases we found ultrasonographic data. If surgery was performed within 6 hours after injury (13 cases), postoperative visual acuity outcomes were generally better than if the operation was carried out at a later time, but there was no significant difference ($p = 0.11$) between the group with a degree of injury OTS 1 - 2 ($p = 0.65$) and the group with a degree of injury OTS 3-4. The foreign body surface was indicated in 26 cases (83.9 %) and was greater than or equal to 4 mm^2 in 14 cases (53.8 % of them). Initial visual acuity was below 20/200 in 61.3% of the cases. 12 patients (38.7 %) achieved visual acuity ranging from light perception to hand movements, 7 patients (22.6 %) had visual acuity better than hand movements, but not more than 20/200, and in the remaining 12 patients (38.7 %) BCVA was better than 20/200. The mean preoperative visual acuity for all patients in decimals was 0.3 ± 0.4 SD (logMAR 0.5 ± 0.36 SD).

Follow-up ranged from 1 to 34 months with a mean of 4.5 months. Subsequent to surgical treatment over a mean follow-up of 2.5 months, only one patient reached a visual acuity of light perception (3.2%), 5 patients BCVA reached a visual acuity of 20/200. In the majority of patients (25, or 80.64 %) the best corrected visual acuity was more than 20/200 (an average of 0.7 ± 0.4 SD, 0.16 ± 0.45 logMAR). After 2.5 months (± 3.9 SD), the best postoperative visual acuity for all patients was 0.6 ± 0.4 SD (logMAR 0.24 ± 0.37). For the group of patients with an OTS score of 1-2 the average BCVA was 0.31 ± 0.30 SD (logMAR 0.51 ± 0.52). By contrast, patients with OTS 3-4 reached a visual acuity of 0.84 ± 0.11 (SD ± 0.075 logMAR 0.96). We compared each OTS group together (Figure 17) and evaluated significant differences. The comparison of postoperative BCVA of patients between the two groups of OTS 1-2 and 3 - 4 showed that postoperative best corrected visual acuity was significantly better for ocular injuries with a higher OTS score ($p = 0.000095$). Regardless of OTS score, good preoperative visual acuity (20/200 or better) (83 %) was connected with postoperative visual acuity of 20/40 or better ($p = 0.002$).

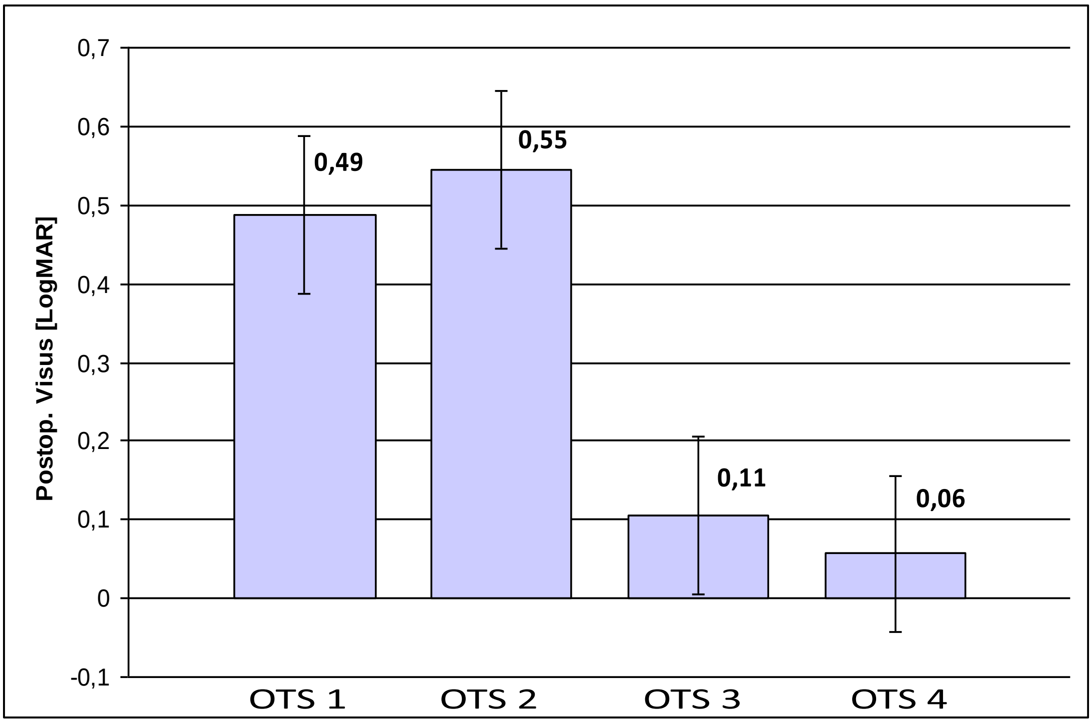


Figure 17: Comparison of postoperative visual outcomes between different OTS groups P values: p=0,08 (OTS 1-4); p=0,03 (OTS 2-3); p=0,005 (OTS 2-4) (Maneschg OA et al.; Klin Monatbl Augenhd. 2011 Sep; 228:801-7).

The postoperative visual acuity was also compared to the size of the foreign body. The size of IOFBs was reported and documented in 26 patients. We found that in the case of injuries with small foreign bodies (< 4 mm ^{2}) the postoperative BCVA (0.85 ± 0.31 SD or logMAR 0.07 ± 0.51) was significantly better than in injuries with larger intraocular foreign bodies (visual acuity 0.25 ± 0.36 SD; logMAR 0.60 ± 0.44; p = 0.002948). In 21 cases, the foreign body was located in the vitreous cavity. For smaller IOFBs with a size <4 mm^2 the postoperative BCVA achieved values of 0.70 ± 0.39 SD (logMAR 0.26 ± 0.62), in the second group with larger foreign bodies > 4 mm^2 the BCVA was 0.26 ± 0.25 SD (logMAR 0.92 ± 0.26 SD), (p = 0.043).

The presence of vitreous hemorrhage influenced the postoperative BCVA (0.37 ± 0.4 SD, 0.77 ± 0.83 logMAR) significantly in contrast to patients who did not refer bleedings in vitreous body (0.81 ± 0.14 SD, 0.5± 0.17 logMAR) (p = 0.024).

In all cases, an intravitreal antibiotic was administered intraoperatively: In eight cases, cefuroxime (1 mg / 0.1 ml), in other eight cases amikacin (0.4 mg / 0.1 ml), in 7 cases tobramycin 1mg / 0.1 ml, in 4 cases vancomycin (1 mg / ml), in two cases ceftazidime alone (2.25 mg / mL) and in one case amikacin combined with cefuroxime. In one case, despite of the intraoperative administration of ceftazidime, POE occurred (3.22 %) 3 days after successful surgical treatment. In this case, the IOFB was localized in the posterior segment and was removed after 12 hours. Other postoperative complications included retinal detachment (9.67%) and PVR 2 months after vitrectomy (3.22%).

5.5 Accuracy of CT volumetry for measurement of IOFB

The CT - volumetric values of 11 IOFBs were in average 68.03 ± 90.1 mm ³. The foreign bodies were preserved in a very good state. The studied foreign bodies were metallic materials or metal alloys, 9 of them were magnetized. All were stainless, there were no adhesive residues of the documentation backing. The measurements determined by water displacement amounted to averagely 64.1 ± 87.5 mm ³ (Figure 18). However, no significant differences were found between in vitro measurement and CT volumetric size (Wilcoxon, p=0.07). When foreign bodies were compared pairwise, the difference was between a lay minimum of 0.2 mm ³ and a maximum of 17 mm ³. Percentually there was a fluctuation range from 0.02 to 16.6 %.

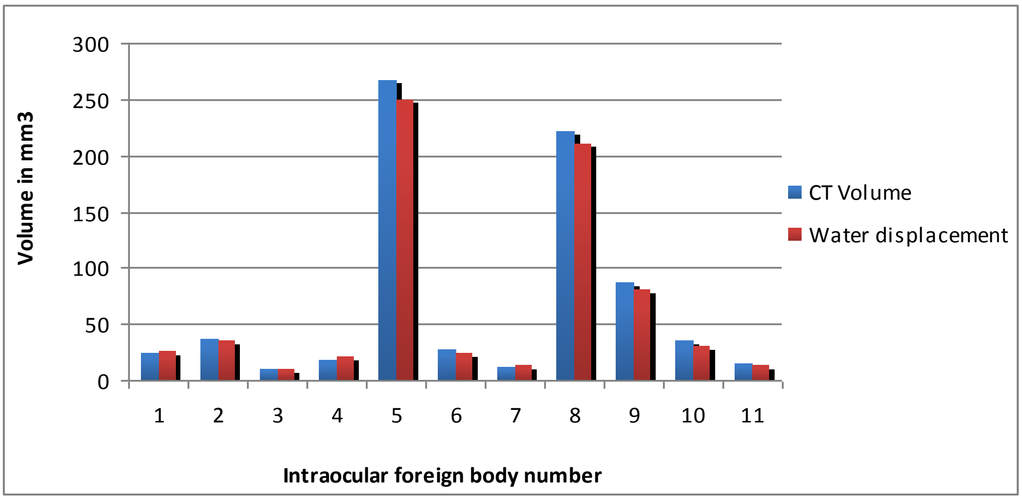


Figure 18: Comparison of calculated IOFB volume by CT volumetry and measured volume by water displacement. There was no significant difference (p = 0.07) (Maneschg OA et al.; Ophthalmologe 2015, 112(4): 359-363.

During study period, we evaluated data of 33 patients with open globe injuries and IOFBs, that had been treated at our department. The average calculated OTS degree was 1.92 and the average age of the patients was 41 years ± 13.45 SD (between 17 and 69 years). Without exception, all patients were male. The average post-treatment period was 7.63 ± 6.16 months (1 to 38 months). During recording, the visual acuity of every patient was determined at the time of admission. The mean BCVA was 0.063 ± 0.16 preoperatively (logMAR 1.2 ± 0.79). All patients were surgically treated by pars plana vitrectomy. After the successful removal of the foreign body, patients achieved an average visual acuity of 0.25 ± 0.2 SD (logMAR 0.6 ± 0.69) after a mean of 3.2 ± 1.3 months.

The 33 present intraocular foreign bodies were divided into 3 groups:

- Group 1 (<15 mm ^{3}, 15 cases): the average preoperative BCVA was 0.16 ± 0.17 (logMAR 0.78 ± 0.76), after surgery the mean best corrected visual acuity achieved 0.36 ± 0.23 (logMAR 0.44 ± 0.64).

- Group 2 (16-35 mm ^{3}, 9 patients): The BCVA values were 0.04 ± 0.22 (logMAR 1.42 ± 0.66) before surgery, postoperatively 0.29 ± 0.18 (logMAR 0.54 ± 0.74) respectively .

- Group 3 (> 35 mm ^{3}, 13 cases): the average preoperative BCVA was 0.02 ± 0.27 (logMAR 1.77 ± 0.56), after vitrectomy 0.07 ± 0.21 (logMAR 1.13 ± 0.67). (Figure 19)

The comparison of the preoperative visual acuity of group 1 and group 2 showed a significant difference (p = 0.031824), but postoperative visual acuity values were not different in comparison (p = 0.811483). When comparing group 2 and 3 we did not find statistically significant differences (preoperative BCVA p = 0.1827 and respectively postoperative BCVA p = 0.0615). Between groups 1 and 3 there were significant differences in preoperative and postoperative visual outcomes (p = 0.00084 and respectively p = 0.0098). Therefore, clinical outcomes were significantly better in injuries with small IOFBs measuring <15 mm3 (p=0.0098).

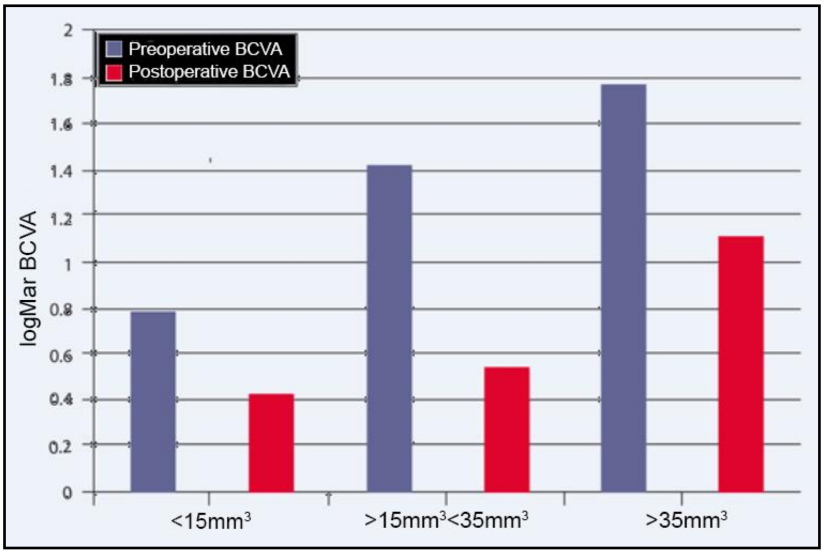


Figure 19: Correlation between pre- and postoperative BCVA and calculated volume of IOFBs by CT volumetry. (Maneschg OA et al.; Ophthalmologe 2015, 112(4): 359-363)

Acute onset endophthalmitis was a complication described in patient's data (2 cases, 5.4 %). Twelve patients indicated that they had suffered the injury while working, but it was not ascertained whether the affected patients had been wearing appropriate protective clothes and safety goggles at the time of eye injury at the workplace.

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6. Discussion

6.1 Evaluation of data on endophthalmitis in Hungary

Postoperative endophthalmitis is the most common type of endophthalmitis [27; 105]. Based on our data from the National Health Insurance Fund in Hungary, the incidence of endophthalmitis following cataract surgery in Hungary during the 8-year period from 2000-2007 was slightly lower (0.058%) than in other developed countries (0.093%) [13]. Rusher, Gyetvai et al. [27] evaluated data on postoperative endophthalmitis in Szeged between 2000 and 2005. The authors describe an incidence for POE of 0.22%. After cataract surgery (phacoemulsification and ECCE), incidence was about 0.18%, but no difference was described between the two surgical techniques [27]. We also analysed reported data on endophthalmitis from patients we treated at the Department of Ophthalmology of the Semmelweis University, Budapest. In the same period (2000-2005), we found 23 cases of POE after 13803 performed cataract surgeries. The incidence was similar to Gyetvai et al. and was calculated with 0,16 %. Time of onset primarily described to have occurred within7 days after cataract surgery (Szeged 51.2%, Budapest 47.7%). The mean age of patients in Szeged was 70.6 ± 4,9, 26.8 % of them also suffered from diabetes. In Budapest, patients were 70,39 years ±14,9 old. In both cities, the most commonly isolated bacteria from vitreous specimen was *staphylococcus spp.* (29.3% and 39.5 % respectively). At our Department, 84 patients were treated because of POE in the mentioned period, in 40 cases we performed an urgent pars plana vitrectomy immediately after admission. Visual outcomes were analysed after surgery. The prognosis was better after cataract surgery. 85 % of the patients reached more than 0.5 decimal BCVA after ECCE or phacoemulsification surgery. Poor prognosis was observed after keratoplasty and trabeculoplasty.

Appropriate hygienic precedures before and after surgery are fundamental in reducing the risk of POE. Bausz et al. [107] examined bacterial contamination during cataract surgery. Before instilling povidone iodide in the conjunctiva they found positive bacterial culture in 21,7 %, after using povidone iodide in only 4.1%. The most common bacterium was *staphylococcus spp*. The technique used for IOL insertion with injector or with forceps did not influence the incidence of positive cultures. Consistent with ETDRS guidelines, the use of povidone iodine significantly reduces the risk of onset of POE [4; 31; 33]. A correct and prompt diagnosis would also improve the clinical outcome. Furthermore, the Endophthalmitis Vitrectomy Study Group (EVSG) recommends vitrectomy as the first choice of treatment in case of massive affection of vitreous body or in case of progression [38]. Current guidelines in Hungary (published on 31th Dec 2008) recommend the following: „..after diagnosis firstly administrate intravitreal antibiotics, in case of progression refer to a tertiary eye care departments. In accordance with EVS perform vitrectomy in case of severe vision loss or absence of red light reflex. If there is no improvement after 24 hours of injection of antibiotics, further delay of vitrectomy may lead to definitive severe vision loss…" [107]. Also in case of acute onset POE the ESCRS recommends an urgent (within a few hours), *total*, 3 port vitrectomy as „golden standard" combined with intravitreal antibiotics. In cases where no vitrectomy can be performed, a single intravitreal injection of 1 mg vancomycin and 2 mg ceftazidim may successfully treat the POE and reduce the risk of severe vision loss („silver standard") [34; 108].

Postoperative endophthalmitis is still a dangerous complication after open globe surgeries. Our data in Hungary confirm that the number of postoperative endophthalmitis cases underwent a significant decrease in Hungary in this 8-year period, indicating the increasing level of eye care. Simultaneously it highlights the fact that improving of hygienic standards further and applying adequate immediate treatment may reduce the risk of irreversible severe vision loss and may improve the prognosis of POE.

6.2 Ultrasound examination in POE

Ultrasound examination is considered a very sensitive and specific method in POE after cataract surgery [25; 26]. The present ultrasound data in our retrospective study describes the development and morphology of post-cataract endophthalmitis in 81 patients. This study, conducted at one single center over a period of 6 years, shows a very broad clinical spectrum of patients with endophthalmitis after cataract surgery. The incidence of post- cataract endophthalmitis in the operated patients at our clinic is in the line with the European averages [5; 14]. In other studies POE were reported with a frequency of 0.04 to 0.7 % after cataract surgery, of 0.27 % after secondary IOL - implantation with scleral fixation and of 0.2-0.7 % after pars - plana - vitrectomy [4; 5, 110]. Although in the last 40 years the incidence of endophthalmitis after cataract surgery has been declining and in the 90's it was 0.08 %, a slight increase was observed from 2000 to 2003 (0.26 %) [11, 27; 105]. The time between surgery and the incidence of endophthalmitis was in the present work very variable. In 77.7 % of all cases with POE due to cataract surgery, endophthalmitis occurred within 6 weeks postoperatively. This result is comparable with the study by Wisniewski et al. [16]. Our study revealed the typical findings which were often also observed in other studies on postoperative endophthalmitis [13; 25]. In our results, we showed that the occurrence of retinal and / or choroidal detachment (combined 16%) and the separation of the posterior vitreous membrane (combined 22 %) were more common in acute and subacute POE after cataract surgery. A change in the echogenicity of the vitreous, the so-called "Vitreous threshold", which may change with increasing reflectors (e.g. increase of cells) in the vitreous cavity, is an early sign of a vitreous involvement during endophthalmitis, and is commonly found using B-scan echography. Because of insufficient data in ultrasonographic documentation, we were not able to evaluate retrospectively this important sign. Retinal detachment (4.9%) was found much more frequently in our study than in other authors (1%) [16]. In contrast, studies of MP Dacey et al. [25] and Marchini et al. [111], showed similar results regarding the imaging of membranes, lacunae and detachment of the posterior hyaloid membrane. In our retrospective study, posterior eye wall thickness was the same for acute, subacute and chronic POE due to cataract surgery. We know that an increase of PEWT is an important sign of inflammation of the posterior pole [26]. Ultrasonographic imaging of increased thickness of the posterior wall and dense organization of the vitreous can be useful in the clinical evaluation, prediction, and treatment of postoperative endophthalmitis.

6.3 SD-OCT examination in patients after successful management of acute POE

For severe postoperative endophthalmitis with severe vision loss, vitrectomy seems to be the first choice of treatment [38] but empiric treatment with broad–spectrum antibiotics is also important for successful clinical outcomes [34; 112]. The aim of this study was to assess the clinical and morphological changes in the retina and choroid long time after postoperative endophthalmitis treated by PPV.

The introduction of spectral domain optical coherence tomography brought a series of improvements in comparison to time domain OCT [101]. In the last 3-4 years, new approaches and technical developments opened new ways in optical coherence tomography and options for examination of retinal and choroidal structures [112]. The Spectralis OCT system is one of the numerous commercially available SD-OCT instruments [91; 94], being the first one capable of performing enhanced depth imaging (EDI). Choroidal imaging may possibly become important, since ocular and systemic disorders related to vascular changes can be associated with significant visual loss. Besides fundoscopy and angiography being the standard procedures for examining the retina in cases of presumed vascular pathologies, recent SD-OCT studies showed that vascular disorders may also cause microstructural changes in the choroid [89; 113; 114]. Other studies using EDI technology revealed new data about deeper structures of the optic nerve head (ONH) and the choroid [93].

In the present study involving eyes with postoperative endophthalmitis, no differences were detected in the thickness of macular retinal layers along with macular volume. Retinal thickness is one of the major treatment criteria for age-related macular degeneration or diabetic macular edema [92; 115]. Apart from this, several authors reported retinal structural abnormalities in various retinal diseases, such as acute zonal occult outer retinopathy-complex diseases [116], epiretinal membranes [117], retinitis pigmentosa or cone dystrophy [118] using SD-OCT and they found significant alterations in the thickness of the outer nuclear layer (ONL). Our patients enrolled in the study reported neither diabetic macular edema nor severe aged-related macular degeneration alterations (AREDS 3 or higher classification). The investigation of ultrastructural photoreceptor abnormalities in the retina was not the aim of our study; our examinations focused on the deeper structures of the retina-choroid complex.

With regard to RNFL thickness measurements there was no significant difference between eyes after endophthalmitis and fellow eyes. Recent studies showed that SD-OCT has a high accuracy and reproducibility in ONH and RNFL measurements in glaucoma [93; 94]. Patients with glaucoma were excluded from our study in order to eliminate false data of RNFL thickness due to glaucoma. According to our observations, RNFL thickness and macular retinal thickness results were tendentially decreased compared to the study eye without reaching statistical significance. Further studies with more patients may support our results.

Since the publication of the first report of EDI-OCT, OCT imaging of the choroid has attracted the interest of clinicians and encouraged further studies of the choroid using EDI-OCT. EDI is an acquisition software option which automatically captures a high sensitive cross-sectional image of the choroid close to the „zero delay line” [100]. With increasing depth into tissue, echoes are more difficult to discern from each-other. EDI technology provides an increased sensitivity of the spectrometer with a higher frequency modulation and with increased pixel numbers in the line scan camera. We measured choroidal thickness of the macular region in 7 points within a 20º x 20º area. Measurements were performed manually using calipers, perpendicular from the outer edge of the hyperreflective RPE to the inner sclera (choroid – sclera junction). According to histopathological examinations, the choroid measures 0.22 mm in thickness posteriorly [101]. In our study the mean choroidal thickness measurement was comparable, approximately 221.86 ± 28.47 μm. In the subfoveal region, choroidal thickness was 248.1 ± 66.2 μm in control eyes and 215.2 ± 63.4 μm after endophthalmitis, respectively. Margolis et al. and Spaide et al. reported similar measurements (mean subfoveal choroidal thickness was 287 ± 76 μm measured by Spectralis with a sample size of 54 healthy eyes) [96]. An available software used for choroidal mapping and volume measurement (e.g. „Heidelberg Eye Explorer software 5.3”) would also be appropriate to measure choroidal thickness and volume [120]; however, we did not have the opportunity to use this software for the measurements.

In the present study we found a significant thinning of choroidal thickness after endophthalmitis ($p = 0.018$), but there was no correlation with visual function. Furthermore, no significant differences in BCVA were observed in eyes after the healing of postoperative endophthalmitis. The small patient series may explain the insignificancy in visual acuity. The patients were of older age, with a range of 56 to 89 years, one patient had amblyopia (documented also in early childhood) in the control eye which caused the large SD of our BCVA data.

So far, choroidal thickness is not widely used as a major criterion to follow up the treatment of macular or choroidal diseases. As an example, in Vogt-Koyanagi-Harada disease choroidal thickness is reduced after successful steroid treatment and can therefore be an important indicator for the assessment of corticosteroid treatment efficacy [121]. Recent studies also showed a decrease in choroidal thickness in highly myopic eyes [122; 123] which is supposed to be a significant risk for the development of choroidal neovascularisation. Other recently published data showed that macular choroidal thickness is not influenced by intraocular pressure [124]. It has been presumed that choroidal thickness influences the posterior eye wall thickness. Németh et al. found in ultrasound measurements that the ocular wall was thicker in hypotony and patients with exophthalmus, but ocular wall dimensions were smaller in patients with glaucoma [125]. Other measurements with scanning laser Doppler flowmeter showed a reduced retinal microcirculation in myopic and glaucomatous eyes [126]. Guthoff et al. and Németh et al. showed that in healthy persons the thickness of the ocular wall is highly dependent on the axial length of the eye, and that the volume of the wall of the eye is nearly constant [127]. Choroidal thickness may probably not be an absolute indicator for failure or success of treatment for endophthalmitis, but decreased choroidal thickness can explain unexpected clinical outcomes with poor vision. In other inflammations such as anterior uveitis or intermediate uveitis choroidal thickness seems to be unaffected [128]. Our study reports the evaluation of a small case series of patients with postoperative endophthalmitis. As inclusion criteria we evaluated only severe acute post cataract endophthalmitis cases with poor initial visual acuity. Pars plana vitrectomy was performed in each case within 24 hours after the outbreak of endophthalmitis, there were no complications observed either intraoperatively or in the early postoperative period and clear media were obtained in each case within 4 weeks. We found that retinal structure and thickness were not significantly different in both groups even long time after vitrectomy. Fujiwara et al. also showed recently that there were no changes in choroidal thickness after microincision vitrectomy for ERM and macular hole. [129]. Assuming that the retina is more exposed to traumatic events during vitrectomy it may be presumed that choroidal thickness changes were probably due to decreased perfusion caused by the post cataract endophthalmitis. Thus, our findings may also support the thesis that early vitrectomy may be of important benefit for long term clinical outcomes in such cases.

It should be noted that out of 17 patients only 8 specimens provided a positive microbiological culture. In other studies a different range of microorganisms was isolated from vitreous samples (70 - 90%) [129; 130; 131].

In the present study we evaluated retinal thickness, choroidal thickness and major retinal abnormalities after post cataract endophthalmitis. However, our study had some limitations. A larger, prospective series of patients and the detailed evaluation also of the microstructural changes in the outer retinal layers, especially in the external limiting membrane (ELM) and the continuity of the inner segment-outer segment junction (IS/OS junction) would be able to provide more information on visual acuity changes after severe post cataract endophthalmitis. Nevertheless, a larger case series could contribute to a more sophisticated statistical evaluation, for instance a correlation analysis with the timing of surgery, the length of follow up time or some surgical factors, such as posterior hyaloid detachment, type of pathogens and age. Therefore, a further prospective study is warranted.

6.4 Clinical outcomes (prognostic factors) and imaging evaluation in patients with IOFB.

In this work, we wanted to emphasize the particular importance of open globe injuries with intraocular foreign bodies based on a retrospective analysis of data of our own patients. Today we commonly use the so-called BETTs (Birmingham Eye Trauma Terminology) scale for the classification of eye injuries [53]. For the description of penetrating eye injuries and for the assessment the severity of the cases, we used the OTS classification (Ocular Trauma Score) in our study. This system was also developed by the Medical University of Birmingham, Alabama, and is still used by the Register of eye injuries in the USA (United States Eye Injury Registry - USEIR) [55; 56]. Follow up time was 4.5 months on average with a relatively large span (1-34 months), because the patients presented for control examinations at our department with varying frequency. This was in part due to large distances to our hospital, but socioeconomic circumstances also played an important role. Retrospectively, we registered relative afferent pupillary defect from patient's documentation in only one case (3.2%), which is strikingly rare. In other studies of GW Schmidt et al. a relative afferent pupilllary defect in open globe injuries was described more frequently (19 %) and played a significant role in the clinical prognosis [133]. The calculated average postoperative BCVA was comparable to results from other studies [134; 135]. A comparison between the results of patients with low and high OTS grades showed that the postoperative visual acuity depended significantly on the state of the eye at admission ($p = 0.000095$). The comparison between the individual OTS grades also showed significant differences in clinical visual outcomes (OTS 1-4 $p = 0.08$, OTS 2 - 3 $p = 0.03$, OTS 2 - 4 $p = 0.005$). In general, comparable to other studies [47], a good initial visual acuity, guarantees significant improvement in postoperative outcome (p = 0.002). In our work, in 74.2 % of all cases IOFBs were located in the posterior segment of the eye, this is comparable to the frequency described in other epidemiological studies [48]. The fact that in all these cases a vitrectomy was carried out as first intervention for the removal of foreign bodies, and the fact that on average the BCVA improved postoperatively from 0.3 ± 0.4 SD (logMAR 0.50 ± 0.36) to 0.6 ± 0.4 SD (logMAR 0.24 ± 0.37), leads to believe, that the vitrectomy, as initial treatment of these severe eye injuries is of immense importance, especially if the foreign body is located in the posterior segment of the eye. These results are comparable with the work of Brinton et al.[136] and Wani et al.[137]. A direct context between size of IOFB and clinical outcome was also observed (p = 0.002948), even if the IOFB was localized in the posterior segment (p = 0.043), comparable to the data of Jonas et al. [138]. Therefore, it seems that the size of the foreign body is an important, significant prognostic factor for clinical outcome. Another significant factor (p = 0.024) for the clinical outcome is the presence of vitreous hemorrhage. Our results are comparable to Cardillo et al. [63] and Wickham et al. [44] and prove that vitreous hemorrhage is an unfavorable prognostic factor in these injuries (p = 0.003). Other risk factors were age and type of activity. The average age of patients involved in our study was 32.3 ± 13.4 years. Most accidents occurred in a domestic environment, followed by the workplace. Other studies with similar results [44; 49] also show that young employed adults are at higher risk than other population groups. A late postoperative complication that we detected in our study was proliferative vitreoretinopathy in 3.22% of all cases. These results showed less prevalence than in the PVR study by Cardillo et al. [63], wherein the frequency of PVR after ocular trauma was found in 11%, but in injuries with IOFBs only in 1% of the patients.

Comparable to the frequency in the work of Chaudhry et al., we found an acute postoperative endophthalmitis within 3 days after surgery (3.22%) [139]. The prevalence was showed much more common than after elective surgeries such as cataract surgery, which we described in our earlier study. Endophthalmitis after open globe injuries play an important role in the grading of the eye injuries and for the prognosis after healing [51; 53; 55]. Therefore exact imaging methods like ultrasound examination and CT at time of admission are fundamental for the management of these injuries. In the described case of postoperative endophthalmitis, the surgery for the removal of foreign bodies was carried out after merely 12 hours. Jonas et al. [138] showed that a higher prevalence of endophthalmitis goes hand in hand with the removal of foreign body conducted at a late point in time. Since we described only one case, we were not able to statistically confirm this finding. A connection with intraoperatively used antibiotic was not confirmed either. There were no specific guidelines for the choice of intraoperatively used antibiotics. Even though the ESCRS makes recommendations in the prophylaxis for endophthalmitis following cataract surgery, these are not necessarily required in the treatment of these severe eye injuries [33; 37]. Cases of siderosis or sympathetic ophthalmia were not described. Other studies by Zhang et al. [58] give an incidence of sympathetic ophthalmia after open globe injuries with 0.37 %. We describe an onset of postoperative retinal detachment with an average treatment period of 30 months in 9.67% of all cases, this is slightly less frequently than in the study from Chiquet et al. (15%). [140]. Our study is designed in a retrospective manner and therefore it is not a result of a standardized documentation method. Furthermore we were not able to ascertain whether safety glasses were worn at the time of the accident. Other authors described that eye protection was worn in only 6 – 15% of these injuries [134; 141].

6.5 Accuracy of CT volumetry for measurement of IOFB

Computed tomography (CT) is a standard method of examination in open globe injuries with intraocular foreign bodies. Its sensitivity is very high, almost 100%. Compared to other methods of investigation, such as ultrasound or magnetic resonance imaging (MRI), particularly small foreign bodies can be detected by CT. Gor et al. [78] showed that helical CT is the most sensitive method compared to axial CT, MRI and ultrasound, to determine small glass debris. The use of special collimators makes it possible to irradiate a particular scan plane and the radiation is focused precisely on the foreign body [77]. Sometimes highly reflective foreign bodies can lead to flare effects that can complicate the localization of the foreign body in terms of location in the eye, that is why there is always the element of surprise in the treatment of these severe eye injuries.

Several studies have addressed the risk factors in open eye injuries with intraocular foreign bodies. Important factors proved to be initial visual acuity, rapid surgical removal of intraocular foreign body, presence of vitreous hemorrhage, retinal detachment, and presence of relative afferent pupillary defect [44; 53; 55; 135]. The dimensions and the shape of intraocular foreign bodies also play an important role [142] in the clinical outcome. Our measurements confirmed these findings, therefore the size of the IOFBs in addition to other risk factors such as retinal detachment, endophthalmitis, presence of relative afferent pupillary defect and eye rupture seems to be of central importance for the clinical outcome (Fig.19) [44; 53; 135]. In particular, the comparison between smaller and larger foreign bodies (group 1 vs. group 3) showed a significant difference ($p = 0.00084$ and $p = 0.0098$).

In our study, vitreous hemorrhages were found in 43 % of all cases. Vitreous hemorrhage was described as a major risk factor for clinical outcome in several studies [53] and was found similary often in our work. In our study, acute endophthalmitis occurred in 5.4% of the cases as a postoperative complication. This result was somewhat found similary often than in the study of Zhang et al. [58].

CT volumetry, which is already a standard method for preoperative planning in other areas of medicine, is of very high accuracy [82]. The results from our pairwise comparison between CT volumetric values and volumes determined by water-displacement showed no significant difference ($p = 0.07$). Thus we can suppose that CT volumetry can make accurate statements about the volume of intraocular foreign bodies and is important for the clinical outcome. In addition, the three-dimensional representation of the foreign body and the visual reconstruction of the eye and orbit can provide extra assistance in treating these severe injuries.

Open globe injuries with intraocular foreign bodies are typically found at craftsmen [58]; 32 % of our patients reported that they had suffered this injury while working. This points to the importance of appropriate protective gear.

7. Conclusion

In our work we aimed for the understanding of the morphological changes in postoperative endophthalmitis following cataract surgery using modern imaging techniques. Furthermore, our aim was to understand the clinical findings and the follow-up in open globe lacerations with intraocular foreign bodies to be able to make a better prognosis after these severe eye injuries.

In the first part of this thesis, we investigated the epidemiology of endophthalmitis in Hungary, subsequently we evaluated ultrasonographic clinical findings in a large retrospective study. Using the SD-OCT, we also aimed at evaluating potential micromorphological changes in the retina and choroid due to postoperative endophthalmitis.

In the second part of our thesis, we focused on the evaluation of clinical findings in open globe injuries with IOFBs and organized the injuries according to the OTS classification. Finally, we focused on IOFBs special imaging, using CT volumetry to estimate the size of IOFBs and to evaluate its significance as a prognostic factor.

<u>In summary, we have shown the following</u>:

- We have shown the importance of ultrasound in the diagnostics of POE. Our findings not only confirm typical clinical signs known previously, but we also described ultrasonographic differences between acute and chronic post cataract endophthalmitis in a very exact manner. Two findings detected by initial echography were associated with acute and subacute endophthalmitis: dense vitreous opacities and detachment of posterior vitreous limiting membrane.

- We have shown the usefulness of high resolution Spectral Domain Optical Coherence Tomography to detect morphological changes in the choroid after vitrectomy due to postoperative endophthalmitis. We found that choroidal thickness decreased significantly after endophthalmitis, but there was no functional correlation with the changes in choroidal microstructure. Furthermore, the development of epiretinal membranes may have been associated with either vitrectomy or endophthalmitis in the history. However, these structural findings have no influence on the visual acuity and clinical outcome and showed, that successful treatment may guarantee good clinical results even long after this severe postoperative complication.

- We retrospectively analysed data of patients affected by open globe injuries with intraocular foreign bodies. Using OTS classification we confirmed that postoperative BCVA was significantly better for ocular injuries with a higher OTS score, so that acceptable visual results could be achieved after the removal of posterior segment IOFBs by vitrectomy.

- We demonstrated that the use of CT volumetry is an accurate method for the measurement of IOFBs. Exact data about the size and measurement of volume are also an important factor for the prognosis of clinical outcome in open ocular injuries with IOFBs, and CT volumetry can also provide important information about the localization of IOFBs.

Our results are highlighting the importance of modern imaging techniques in the diagnosis, management and prognosis of postoperative endophthalmitis and open globe injuries with intraocular foreign bodies.

8. Summary

Even though postoperative endophthalmitis following cataract surgery has become a rare complication in the last decade, it is a very severe disease that can lead to permanent severe vision loss and imposes a heavy burden on ophthalmological societies and patients. The introduction of new cataract surgery techniques and standard hygienical pre-, intra and postoperative procedures significantly decreased the incidence of POE in Hungary in the last 15 years. Ultrasound examination is a standard procedure in the diagnostics of postoperative endophthalmitis. This rapid, noninvasive, safe imaging method shows typical findings especially in acute onset POE. Therefore, it does not only indicate the necessity to perform early vitrectomy, but it is also very useful for follow-up after performed surgical treatment. Another application of imaging techniques in POE was the use of Optical Coherence Tomography. The increased utilization of SD-OCT helped to better understand the micromorphological structures in the retina and choroid. Using enhanced depth imaging (EDI) technology in SD-OCT, we found that choroidal thickness in affected eyes decreased significantly after the successful management of POE, compared to the contralateral healthy pseudophakic eye, but we also demonstrated that these findings did not influence the clinical outcome. Vitrectomy performed at an early stage seems to be fundamental to guarantee good postoperative results even long term after this severe postoperative complication.

Retrospectively, we evaluated clinical data and elaborated prognostic factors of open globe injuries with intraocular foreign bodies. Vitreous hemorrhage, detachment of the retina, good initial visual acuity and presence of endophthalmitis at time of admission are significant for the clinical outcome. Furthermore, we analysed the size of IOFBs as prognostic factor and confirmed its importance for the prognosis. In the future, the detection of the size of IOFBs, using CT volumetry can provide important information for the planning of surgeries to remove the IOFBs. We evaluated volumetrical data with measurements of water displacement and thereby the accuracy of this imaging method.

Exact imaging procedures in diagnostics of postoperative endophthalmitis and open globe injuries with IOFBs may help the ophthalmologist to better plan the surgical treatment, to provide effective care and to give a better prognosis after the healing of these severe eye injuries.

9. Összefoglaló

Az utóbbi évtizedben a szürkehályogműtétet követő endophthalmitis (POE) ritkán előforduló komplikáció, azonban igen súlyos és veszélyes szövődmény a maradandó látáskárosodás tekintetében, ezáltal jelentős probléma a szemész társadalom és a betegek számára egyaránt. Az új sebészeti technikák bevezetése az utóbbi 15 évben szignifikánsan csökkentette a POE incidenciáját Magyarországon. A posztoperatív endophthalmitis diagnózisában az ultrahangos vizsgálat standard módszernek számít. Ez a gyors, noninvazív, biztonságos képalkotó eljárás tipikus jellemzőket mutat különösen az akutan kialakuló POE esetében. Így nem csupán a korai vitrectomia szükségességét mutatja ki de egyben igen hasznos az elvégzett sebészi beavatkozás utánkövetésében is. Egy másik képalkotó eljárást is használtunk a POE esetében, az Optikai Koherencia Tomográfiát. A Spectral domain (SD)-OCT használata jelentősen segítette a retina és a choroidea mikromorfológiai struktúráinak jobb megértését. Az SD-OCT továbbfejlesztett mélységi képalkotás (EDI) technológiáját - használva azt találtuk, hogy a POE sikeres kezelését követően a choroidea vastagsága szignifikánsan csökkent az érintett szemek esetében összehasonlítva az ellenoldali, egészséges pseudophákiás szemmel, ugyanakkor nem volt hatással a klinikai eredményekre. A korai vitrectomia továbbá alapvető fontossággal bír a jó posztoperatív eredmények elérésében.

Az intraokuláris idegentesttel járó sérülések klinikai adatait és alaposan kidolgozott prognosztikus faktorait retrospektív módon értékeltük ki. Üvegtesti vérzés, retina leválás, jó kezdeti látásélesség, a felvételkor tapasztalt endophthalmitis mind jelentős tényezők voltak a későbbi funkcionális eredményekben. Analizáltuk az intraokuláris idegentest (IOFB) méretét is és szintén jelentősnek találtuk, mint prognosztikus faktort. Az IOFB méretének meghatározására a CT térfogat elemzés ígéretesnek tűnik a jövőben és fontos információval bírhat az IOFB sebészi eltávolításának tervezésében. Kiértékeltük a térfogat elemzési adatokat a vízkiszorítási mérések alapján és így pontosítottuk a képalkotási módszer hitelességét.

A pontos képalkotás a posztoperatív endophthalmitis és az IOFB-val társuló behatoló szemsérülések diagnózisában segítheti a szemészt a sebészi beavatkozás megfelelő tervezésében és a hatékonyabb kezelésben egyaránt,így pontosabb prognózist eredményezve ezen súlyos szembetegségek gyógyítását követően.

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11. Publications of the author

11.1. Publications of the author in the scope of the present work

Papers

1) Németh J, **Maneschg O**, Kovács I: „Az endophthalmitis magyarországi adatai 2000 és 2007 között - Data on endophthalmitis in Hungary between 2000 and 2007"; *Szemészet* 148:(2) pp. 42-45. (2011)
2) **Maneschg O**, Csákány B, Németh J: „Ultrasonographische Befunde bei Endophthalmitis nach Kataraktoperationen- Rückblick auf 81 Fälle (Ultrasonographic findings in Endophthalmitis following cataract surgery: a review of 81 cases)"; *Ophthalmologe* 106:(11) pp. 1012-1015. (2009) **(IF: 1.0)**
3) **Maneschg OA**, Resch M, Papp A, Németh J: „Prognostische Faktoren und klinische Ergebnisse in der Behandlung von offenen Augenverletzungen mit intraokularen Fremdkörpern (Prognostic factors and visual outcome for open globe injuries with intraocular foreign bodies)"; *Klinische Monatblätter für Augenheilkunde* 228:(9) pp. 801-807. (2011) **(IF: 0.51)**
4) **Maneschg OA**, Volek É, Németh J, Somfai GM, Géhl Z, Szalai I, Resch MD: "Spectral domain optical coherence tomography in patients after successful management of postoperative endophthalmitis following cataract surgery by pars plana vitrectomy", *BMC Ophthalmol*ogy 14: Paper 76. 8 p. (2014) **(IF: 1.02)**
5) **Maneschg OA**, Volek É, Lohinai Z, Resch MD, Papp A, Korom C, Karlinger K, Németh J: "Genauigkeit und Relevanz der CT Volumetrie bei offenen Bulbusverletzungen mit intraokularen Fremdkörpern (Accuracy and relevance of CT volumetry in open globe injuries with intraocular foreign bodies)", *Ophthalmologe* 112:(4) pp. 359-363. (2015) **(IF 2014; 0,504)**

11.2. Publications of the author outside the scope of the present work

Papers

1) Resch M, Seres A, **Maneschg O**, Pregun T, Papp A, Szabó A, Németh J: “Nehéz szilikonolaj a retinaleválás sebészetében - Haevy silicon oil in retinal detechment surgery”; *Szemészet* 147:(3-4) pp. 155-161 (2010).
2) Marsovszky L, **Maneschg O**, Németh J, Resch MD: „Hornhaut Konfokal-Mikroskopie bei einer bilateralen Augenverletzung mit multiplen kornealen Fremdkörpern (Confocal microscopy after multiple corneal foreign body injury)“ *Spektrum der Augenheilkunde* 25:(3) pp. 231-233 (2011) **(IF: 0,274)**
3) Resch MD, Takáts J, Csákány B, Szabó A, **Maneschg O**, Papp A, Németh J: “Retinal thickness measurements with optical coherence biometry and optical coherence tomography” *Spektrum der Augenheilkunde* 28:(3) pp. 121-125 *(*2014)
4) Géhl Z, Kulcsár K, Kiss HJM, Németh J, **Maneschg OA**, Resch MD:” Retinal and choroidal thickness measurements using spectral domain optical coherence tomography in anterior and intermediate uveitis”, *BMC Ophthalmology* 14:(1) Paper 103. 7 p. (2014) **(IF: 1.02)**
5) Géhl Z, **Maneschg OA**, Nagy ZZ. Progressive Bilateral Chorioretinitis. *Klinische Monatblätter für Augenheilkunde* Klin Monbl Augenheilkd. In press (2015 Sep 14) (**IF 2013/2014**; **0,504)**

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