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RESULTADOS ANATÓMICOS E FUNCIONAIS APÓS O TRATAMENTO MÉDICO E/OU CIRÚRGICO DAS ENDOFTALMITES AGUDAS NOS ÚLTIMOS 7 ANOS NA REGIÃO CENTRO DO PAÍS

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ANATOMIC AND FUNCTIONAL RESULTS FOLLOWING MEDICAL AND/OR SURGICAL TREATMENT OF ACUTE ENDOPHTHALMITIS IN THE LAST 7 YEARS IN THE CENTRAL REGION OF THE COUNTRY

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Acronyms

AEE: Acute exogenous endophthalmitis

CF: Counts fingers

EVS: Endophthalmitis Vitrectomy Study

ESCRS: European Society of Cataract and Refractive Surgeons

HM: Hand-movements

IVI: Intravitreal injection

LogMAR: Logarithm of the minimal angle of resolution

LP: Light perception

LS: Letter score

PPV: Pars plana vitrectomy

RD: Retinal detachment

SE: Snellen equivalent

Resumo

Introdução: A endoftalmite é uma infeção intraocular, geralmente de causa exógena. É uma doença rara, mas possivelmente catastrófica que pode conduzir à cegueira irreversível do olho afetado. O principal objetivo do presente estudo consiste em avaliar os resultados do tratamento da endoftalmite aguda exógena, inferindo sobre o papel da vitrectomia via pars plana no mesmo. Pretende-se ainda estudar o impacto de diferentes variáveis pré- e intraoperatórias nos resultados funcionais e anatómicos desses doentes.

Métodos: Neste estudo observacional retrospetivo, foram incluídos 83 doentes submetidos a injeção intraocular de antibióticos com/sem vitrectomia via pars plana para tratamento de endoftalmite aguda exógena no Centro de Responsabilidade Integrada de Oftalmologia do Centro Hospitalar e Universitário de Coimbra, entre janeiro 2016 e junho de 2022. Todos os doentes mantiveram um seguimento mínimo de 6 meses. As características demográficas, clínicas, terapêuticas e relacionadas com o seguimento desses doentes foram registadas e analisadas.

Resultados: A mediana de idade da população estudada foi de 77 anos (38-95) à data de início dos sintomas e o olho direito foi acometido em 51.81% dos casos. A mediana da acuidade visual pré-tratamento foi de 2.28 LogMAR (1.98-2.70). Houve melhoria significativa ao considerar a última acuidade visual dos doentes estudados (P < 0.001), com melhoria mediana de -0.50 LogMAR (-1.68-0.00) e resultado mediano da acuidade visual final de 0.80 LogMAR (0.20-2.28). As duas principais causas responsáveis pelos casos de endoftalmites foram a cirurgia de catarata e as injeções intravítreas. As complicações incluíram 11 descolamentos de retina, 7 eviscerações, 3 edemas maculares, 2 descompensações da córnea e 2 casos de glaucoma. A melhor acuidade visual pré-tratamento e a variação da acuidade visual antes e após o tratamento foram estatisticamente semelhantes entre o grupo submetido a injeções isoladas e o grupo submetido a injeções e vitrectomia combinadas. As melhores acuidades visuais finais registadas foram significativamente diferentes entre os dois grupos.

Conclusão: Embora a endoftalmite aguda represente uma condição grave com possíveis resultados catastróficos e maus prognósticos visuais, uma melhoria nos resultados de acuidade visual foi registada em 71.08% dos doentes incluídos neste estudo. Apesar de incluir um grande número de doentes quando comparado com outros estudos recentes neste âmbito desenvolvidos num único centro, não foi possível

demonstrar qualquer superioridade relacionada com o uso generalizado de vitrectomia via pars plana no tratamento de endoftalmite aguda no nosso estudo.

Palavras-chave: Endoftalmite aguda, Injeção intravítrea de antibiótico, Vitrectomia.

Abstract

Introduction: Endophthalmitis is an intraocular infection, usually due to an exogenous cause. It is a rare but possibly catastrophic disease, potentially leading to irreversible blindness in the affected eye. The main objective of the study is to evaluate the treatment outcomes of acute exogenous endophthalmitis, inferring on the role of pars plana vitrectomy in the management of these patients. In addition, we intend to study the impact of different pre- and intraoperative variables on the functional and anatomical outcomes of endophthalmitis patients.

Methods: In this retrospective observational study, 83 patients were included which underwent antibiotic intraocular injection with/without pars plana vitrectomy for the treatment of acute exogenous endophthalmitis at the Integrated Responsibility Center for Ophthalmology of Centro Hospitalar e Universitário de Coimbra, between January 2016 and June 2022. All patients had a minimum follow-up of 6 months. The demographic, clinical, therapeutic and follow-up related characteristics of these patients were recorded and analyzed.

Results: The median age of the studied population was 77 years (38-95) and the right eye was affected in 51.81% of cases. The median pre-treatment vision acuity was 2.28 LogMAR (1.98-2.70). There was a significant improvement when considering the last recorded visual acuity during the patients' follow up appointments (P < 0.001), with a median improvement of -0.50 LogMAR (-1.68-0.00) and median final visual acuity result of 0.80 LogMAR (0.20-2.28). The two major causes responsible for the endophthalmitis cases were cataract surgery and intravitreal injections. Complications included 11 retinal detachments, 7 eviscerations, 3 macular oedemas, 2 corneal decompensations and 2 glaucoma cases. The best pre-treatment visual acuity results and variation of visual acuity before and after treatment were statistically similar between the group submitted to injections alone and the patients which underwent injections and vitrectomy combined. Final best recorded visual acuities were significantly different between the two groups.

Conclusion: Even though acute endophthalmitis represents a serious condition with possible catastrophic outcomes and poor visual prognosis, an improvement in visual acuity results was recorded in 71.08% of patients. Despite including one of the highest numbers of patients in recent single-center studies of this kind, it was not possible to confidently demonstrate any superiority related to the general use of pars plana vitrectomy in the management of acute endophthalmitis in our study.

Introduction

Endophthalmitis is an intraocular infection of bacterial, fungal or, seldom, parasitic etiology. This infection is usually originated by an exogenous cause, but may exceptionally arise endogenously through the hematogenous spread of the microorganisms.[1]

Exogenous endophthalmitis account for more than 90% of reported cases and usually follow ocular procedures, resulting from intraocular surgery or intravitreal injections. They may also be of traumatic origin or associated with infectious keratitis or scleritis.[2-4] This condition can be classified, regarding its presentation, as acute, when its onset lies within the first 6 weeks following the event identified as the origin of the infection, or chronic, when beyond this time frame.[5]

The present study will address acute exogenous endophthalmitis (AEE), with the exception of those originating from infectious keratitis or scleritis.

The incidence of this pathology reported in the literature varies considerably, usually extending between 0.02% and 0.54% depending on the leading cause. However, AEE is more frequent when following penetrating trauma, with its incidence values rising up to 18% after traumatic events of this nature.[6-9]

In AEE, systemic symptoms are not usually found. This condition's clinical manifestations commonly include a marked loss of visual acuity, accompanied by pain and intense conjunctival hyperemia with oedema of the eyelids and cornea. Anterior and posterior segment inflammation is present, with flare and cells in the anterior chamber, many times forming an hypopyon, pupillary inflammatory membranes and vitritis. Symptoms typically arise within 1 week after the originating event/surgery.[6,10]

Gram-positive cocci are the most frequently identified pathogens in AEE, in particular coagulase-negative staphylococci. The frequency of other microorganisms varies depending on geographical factors and on the type of AEE.[1,6]

In the management of this condition, intravitreal antibiotics are the standard of care. Moreover, pars plana vitrectomy (PPV) alongside antibiotic intravitreal injection (IVI) is recommended as "gold standard" by The European Society for Cataract & Refractive Surgeons (ESCRS), whenever a vitreoretinal surgeon and operating room are available.[1] However, this broader use of PPV is not favored by all clinicians and evidence in recent studies is conflicting.

Since AEE represents an ophthalmological emergency, often resulting in irreversible blindness of the affected eye, it is of utmost importance to optimize the approach to this pathology in order to safeguard the patient's quality of life. Thus, this study aims to evaluate the anatomical and functional treatment outcomes of AEE in the selected patients, establishing a comparison between the two most relevant treatment procedures (antibiotic intraocular injection with or without PPV) and further inferring on other pre-treatment, treatment-related and post-treatment factors related to the final outcomes of the patients.

Centro Hospitalar e Universitário de Coimbra is the most differentiated healthcare facility in the center region of the country, which has a population of around 2 million inhabitants, and includes a general emergency department open 24 hours a day. Its Integrated Ophthalmology Responsibility Center is the only in the region with the capacity to perform PPV, which is why it receives practically every case of endophthalmitis diagnosed in hospitals in this region. For this reason, our casuistry adequately reflects the reality of this pathology in the Portugal's central region.

Methods

Study design

A retrospective observational study was carried out at the Integrated Ophthalmology Responsibility Center of Centro Hospitalar e Universitário de Coimbra, which included patients who underwent antibiotic intraocular injections with/without PPV for the treatment of AEE, between January 2016 and June 2022, with a minimum follow-up of 6 months.

The patients were selected, consecutively, from a pre-existing database that contained the clinical information necessary to carry out the study, introduced by the doctors who operated and/or followed them.

Study population

All patients undergoing treatment for AEE preceded by an invasive intraocular procedure or open ocular trauma, with a minimum follow-up of 6 months, were included. All patients diagnosed with endogenous endophthalmitis or endophthalmitis originated from infectious keratitis or scleritis were excluded. Those who developed symptoms more than 6 weeks after the originating event (chronic endophthalmitis) were also excluded.

Data collection

Prior to data analysis, the database (containing only the sufficient and necessary information to carry out this study) was irreversibly anonymized by eliminating the unique file number, patient name and any other demographic information that would somehow allow the identification of the patients.

The data analyzed included age, sex, laterality, symptoms at time of presentation, etiology of the infection, date of the invasive procedure (surgery or intraocular injection)/open ocular trauma and time elapsed between this date and the symptoms' onset, date of diagnosis, date of tap biopsy for microbial culture, sample used for microbiological culture (vitreous humor/aqueous humor/both), result of the microbial culture, date of administration of each treatment (PPV and intraocularly injected, systemic, topical and subconjunctival antibiotics), antibiotics administered, preoperative best corrected visual acuity, last best corrected visual acuity recorded, number of

intraocular injections and PPVs which patient underwent, intraoperative and post-operative complications.

Best corrected visual acuities normally recorded in Snellen chart measures were converted into logarithm of the minimum angle of resolution (LogMAR) values for statistical analysis. Counts fingers (CF), hand motion (HM), light perception (LP) and no light perception records were substituted with 1.98, 2.28, 2.70 and 3.00 LogMAR, respectively, as described in previous studies.[11,12]

Statistical analysis

A descriptive analysis of the collected data was carried out using summary measures such as median and interquartile range in non-normally distributed variables and proportions in categorical and binary variables. Additionally, as the studied variables were not normally distributed, non-parametric testing was used for the study of pre- and intraoperative predictors. When Spearman correlation tests were used, r-value indicates the Spearman's correlation coefficient. The data was analyzed using IBM SPSS statistical software version 29.0 (Armonk, NY: IBM Corp), and a P value less than 0.05 was considered significant.

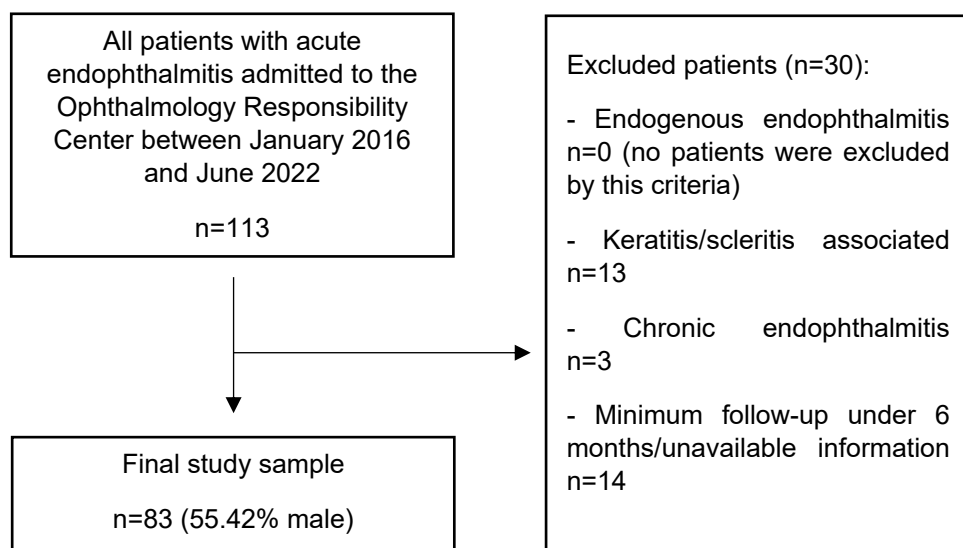This study was submitted and approved by the local ethics committee (OBS.SF.159-2022).

Fig. 1. Flow diagram of study participants

Results

This study included 83 eyes from 83 patients, 46 male (55.42%). The right eye was affected in 51.81% of cases (n=43). The median age of the studied population was 77 years (38-95) at the time of symptoms' onset.

The median pre-treatment vision acuity was 2.28 LogMAR [1.98-2.70; Snellen equivalent (SE): HM]. There was a significant improvement when considering the last recorded visual acuity during the patients' follow up appointments ($P < 0.001$), with a median improvement of -0.50 LogMAR (-1.68-0.00) and median final visual acuity result of 0.80 LogMAR [0.20-2.28; SE: 20/125; Letter score (LS): 45].

An improvement between the best visual acuity at presentation and the best visual acuity record at the patient's last follow-up appointment was recorded in 71.08% (59/83) of patients. This visual acuity results were the same in 9.64% (8/83) of cases and 19.28% (16/83) presented with worse final visual acuity results than the ones recorded at time of diagnosis.

The median follow-up period was 12 months (6-34).

Pre-treatment factors

The major factor related to final visual acuity results was the visual acuity recorded at presentation ($P < 0.001$), as results showed a strong correlation between worse presenting visions and worse vision outcomes (r = 0.684).

The majority of cases were related to intraocular procedures, which accounted for 97.59% (81/83) of all recorded cases. Cataract surgery and IVIs were the two major procedures represented, with 48.15% (39/81) and 45,68% (37/81) respectively. We also included 3 cases following trabeculectomy for glaucoma treatment (3.70% of all procedure related AEEs), 1 case following vitrectomy (1.23%) and 1 other case following Descemet stripping endothelial keratoplasty (DSAEK) (1.23%). Two cases related with penetrating ocular trauma were also recorded, accounting for 2.41% of all AEE cases.

Median symptom onset time was 4 days (2-10) following intraocular procedure or trauma. The most prevalent symptoms at time of presentation were blurred vision/decreased visual acuity, eye pain and conjunctival hyperemia, present in 80.72% (67/83), 55.42% (46/83) and 30.12% (25/83) of patients, respectively.

Other signs and symptoms were recorded at lower frequencies, including purulent secretions, hypopyon, macular oedema, anterior chamber flare, epiretinal membranes, eye floaters, photophobia, and vitreous hemorrhage.

Symptom onset time was the same between IVI-related cases and cataract surgery-related AEEs, with a median flare-up time of 4 days (2-21 IVI group; 2-6 cataract surgery group). The time taken from the originating event/procedure to symptom onset had no significant effect in baseline (P = 0.115) or post-treatment visual acuities (P = 0.935), nor in the visual acuity variation (P = 0.072).

The great majority of patients started treatment on the day of presentation/diagnosis (median: 0 days; 0-0).

The median interval from symptom onset to intraocular antibiotic injection treatment was 2 days (0-3). For PPV, it was 4 days (2-6). Regardless of the first treatment to be implemented (antibiotic injections alone or combined with PPV), patients who underwent IVIs had a median interval between the symptom flare-up and treatment initiation of 2 days (0-3), the same as patients with cataract surgery related AEEs. For trabeculectomy and trauma-related cases, the median intervals were 6 days (0-6) and 2.5 days, respectively. Both the vitrectomy-related case and the case following DSAEK had a 1-day interval between symptoms flare-up and treatment initiation.

Briefness in treatment initiation from the time of symptom onset was not significantly associated with a better post-treatment visual acuity (P = 0.366), nor was it related with the number of cases resulting in evisceration of the affected eye (P = 0.392).

For systemic antibiotic administration, the median interval from symptom onset to treatment initiation was the same as for topical and subconjunctival antibiotics: 1 day, with and interquartile range of 0-3 for systemic and subconjunctival antibiotics and 0-4 for topical antibiotics.

Median visual acuity at presentation for the cataract surgery group and the IVI-related groups was the same with 2.28 LogMAR (1.98-2.70; SE: HM). Final recorded visual acuity median values were 1.00 LogMAR (0.40-2.28; SE: 20/200; LS: 35) for cataract surgery related AEEs *versus* 0.40 LogMAR (0.10-2.49; SE: 20/50; LS: 65) for post-IVI AEEs. Post-trabeculectomy AEEs had a median visual acuity at time of presentation of 2.70 LogMAR (2.28-2.70, SE: LP) and a median final visual acuity of 2.28 LogMAR (1.98-2.28; SE: HM). Visual acuity at time of presentation was 2.28 LogMAR (SE: HM) and 1.98 LogMAR (SE: CF), for vitrectomy and DSAEK-related AEEs, respectively, and final visual acuity records were 1.98 LogMAR (SE: CF) (vitrectomy) and 0.52 LogMAR (SE:

20/63; LS: 60) (DSAEK). For open-trauma-related AEEs the median visual acuity at presentation was 1.02 LogMAR (SE: 20/200; LS: 35). The median final visual acuity value was 0.05 LogMAR (SE: 20/25; LS: 80).

There was no significant difference regarding the visual acuity results at presentation between these groups (P = 0.310). The same can be said for the post-treatment visual acuity results (P = 0.179) and variation of visual acuity before and after treatment (P = 0.979).

Treatment-related factors

All patients were submitted to intraocular antibiotic injections.

Antibiotic IVIs were administered in 82 patients. Both ceftazidime 2.25 mg/0.1 mL and vancomycin 1 mg/0.1 mL were injected in the majority of cases, corresponding to a total of 98.78% (81/82), but 1 patient was submitted to vancomycin 1 mg/0.1 mL injection alone due to cephalosporin allergy. Following positive culture and antimicrobial susceptibility testing, one patient had cefazoline 2 mg/0.1 mL injected after 2 previous injections of ceftazidime + vancomycin, to better fit the microbiologic sensibility.

Cefuroxime injected (1.0 mg/0.1 mL) in the anterior chamber of the eye in 2.41% (2/83) of patients. In one of them, this was the only antibiotic injection administered, since he was submitted to simultaneous PPV with silicone oil tamponade for intra-operative retinal detachment (RD).

The median number of antibiotic intraocular injections was 1 (1-2), as 54.21% (45/83) had 1 injection, 38.55% (32/83) had 2 injections and 7.23% (6/83) had 3 injections. For cases that required more than one intraocular antibiotic injection, the median interval from the first injection to the second one was 2 days (2-3) and from the second to the third injection was 1.5 days (1-2.5).

The number of injections each patient was submitted to did not significantly correlate to post-treatment visual outcomes nor to the variation of visual acuity before and after treatment (P = 0.211).

Patients submitted to PPV accounted for 73.49% (61/83) of all cases, while antibiotic intraocular injection without vitrectomy were conducted in 26.51% (22/83) of cases. A single PPV was conducted in 96.72% (59/61) of patients, 2 PPVs in 1.64% (1/61) and 4 PPVs in 1.64% (1/61).

When regarding the AEEs cause, we found that in the IVI-related group, 67.57% (25/37) of patients were treated with antibiotic injections alone, while 32.43% (12/37) had injections combined with PPV. In the cataract surgery group, 79.49% (31/39) had antibiotic injections alone and 20.51% (8/39) had injections combined with PPV. All patients in the trabeculectomy, vitrectomy and DSAEK groups were submitted to PPV, whilst no patients on the penetration trauma group were.

The improvement in visual acuity was significant both in the group of patients submitted to intraocular injections alone (P = 0.010) and in the patients submitted to injections and PPV combined (P < 0.001). Recorded visual acuity results and the comparison between the two treatment groups is represented in Table 1.

The variation of visual acuity before and after treatment was statistically similar between the group submitted to injections alone and the group which underwent injections and PPV combined (P = 0.860). The same did not apply to the final recorded visual acuities (median: 0.25 (0.04-2.46; SE: 20/40; LS: 70) *versus* 1.30 LogMAR (0.35-2.28; SE: 20/400; LS: 20), respectively, where there was significant difference between the two groups (P = 0.026).

The median pre-treatment visual acuity in the group of patients submitted to injections alone was 1.98 LogMAR (0.81-2.70; SE: CF) and in the group submitted to injections and PPV combined it was 2.28 LogMAR (1.98-2.70; SE: HM). The difference between the two groups was not statistically significant (P = 0.075).

Table 1. Visual acuity results for patients treated with injections alone and injection + PPV and comparison between the two study groups.

	Injections alone [a]	Injections + PPV [a]	P-value [b]
N (%)	22 (26.51)	61 (73.49)	-
Initial VA (LogMAR)	1.98 (0.81/2.70)	2.28 (1.98/2.70)	0.075
Final VA (LogMAR)	0.25 (0.04/2.46)	1.30 (0.35/2.28)	0.026*
VA Variation (LogMAR)	-0.18 (-1.91/0.01)	-0.72 (-1.58/-0.05)	0.860

* P < 0.05; [a] Data is expressed using median and interquartile range (Q1/Q3); [b] P-value regarding difference between the two treatment approaches, using Independent-Samples Mann-Whitney U Tests; N, number of patients; VA, visual acuity.

PPV treatment managed similar results as intraocular antibiotic injection-only regarding visual acuity variation in patient subgroups with presenting visual acuity under 1.00 LogMAR (SE: 20/200; LS: 35) (P = 0.475), 1.98 LogMAR (SE: CF) (P = 0.358), 2.28 LogMAR (SE: HM) (P = 0.840) and 2.70 LogMAR (SE: LP) (P = 0.376).

From the group of patients who were treated with PPV, 72.13% (44/61) had intraocular antibiotics administered as the first treatment, prior to the PPV, and 27.87% (17/61) were submitted to PPV combined with intraocular antibiotic injection as a first approach. In cases where intraocular injection preceded PPV, PPV was conducted on a median of 2 days after injection (2-3), and at an equal median interval of 2 day from the time of diagnosis/presentation (0.5-3.5).

Systemic antibiotics were administered in 97.59% (81/83) of patients, topical antibiotics in 91.57% (76/83) and subconjunctival antibiotics in 15.66% (13/83). The different antibiotics used are summarized in Table 2.

Table 2. Systemic, topical and subconjunctival antibiotics administered.

Antibiotic	Total (%)
Systemic	
Ciprofloxacin	41 (50.62)
Ceftazidime	29 (35.80)
Ceftriaxone	19 (23.46)
Levofloxacin	4 (4.94)
Trimethoprim/Sulfamethoxazole	2 (2.47)
Cefazoline	1 (1.23)
Amoxicillin	1 (1.23)
Topical	
Ceftazidime	58 (76.32)
Vancomycin	55 (73.37)
Ofloxacin	22 (28.95)
Tobramycin	8 (10.53)
Oxytetracycline	6 (7.89)
Trimethoprim/Sulfamethoxazole	1 (13.16)

Subconjunctival	
Gentamycin	12 (92.31)
Cefuroxime	1 (7.69)

Post-treatment factors

Culture results were recorded in 79.52% (66/83) of all included patients.

Collected culture samples varied among patients. An aqueous sample was collected in 43.94% (29/66) of cases, a vitreous sample in 34.85% (23/66) of cases and both aqueous and vitreous samples in 21.21% (14/66) of cases. Culture positivity was not significantly correlated with the type of collected sample (P = 0.975).

Positive results were obtained in 28.79% of reported cultures. No fungi were detected, with all culture results being bacterial. Only 1 case isolated more than 1 bacteria (positive culture for 2 different gram-positive bacteria).

Gram-positive bacteria were shown in 89.47% of positive cultures, with *Staphylococcus epidermidis* accounting for 40% of all identified bacteria. *Enterococcus faecalis* (20%), *Staphylococcus aureus* (15%) *Streptococcus oralis* (5%), *Staphylococcus haemolyticus* (5%) and *Bacillus subtilis* (5%) were the other gram-positive bacteria detected in culture.

Only 2 cultures were positive for gram-negative bacteria, representing 10.53% of all positive cultures. The two bacteria identified were *Pseudomonas aeruginosa* and *Haemophilus influenzae*, 1 for each patient.

Culture positivity and microorganism identification had no significant correlation with time to symptom onset (P = 0.727 and P = 0.397, respectively), but positivity in culture was associated with worse visual acuity results before (P = 0.04) and after treatment (P = 0.08).

Different growth mediums were used for the recorded cultures. Chocolate-agar and blood-agar mediums were used in all cases before April 2021, with positivity rates of 23.08% (9/39), and brain-heart infusion was used from April 2021 to June 2022, with positivity rates of 37.04% (10/27). Sabouraud-agar was used for fungi culture. The increase in positivity rates was not statistically significant (P = 0.218).

Post-treatment complications were recorded in 28.92% (24/83) of patients and included RD (44.00%, 11/25), evisceration (28.00%, 7/25), macular oedema (12.00%, 3/25),

corneal decompensation (8.00%, 2/25), and glaucoma (8.00%, 2/25). One patient also developed toxic keratitis related to the topical antibiotics administered.

All endophthalmitis complications were recorded in patients submitted to either IVIs or cataract surgery. The IVI group was responsible for 66.67% (16/24) of all complicated endophthalmitis cases, accounting for 6 RDs, 4 eviscerations, 3 macular oedemas, 2 corneal decompensations and 2 glaucoma cases. The cataract surgery group was responsible for 33.33% (8/24) of cases with post-treatment complications (5 RDs and 4 eviscerations, with one patient having both complications). The difference between the two groups was not statistically significant (P = 0.069).

All RDs occurred in PPV-treated endophthalmitis, in which 54.55% (6/11) were intraoperative and 45.45% (5/11) took place after the surgery. RD did not show a significant correlation with the patient's final vision distribution.

The loss of the affected eye was recoded in 6.65% (4/61) of patients submitted to PPV. This percentage increases to 13.64% (3/22) in patients who underwent antibiotic injections alone, but this relation was not statistically significant (P = 0.306).

Discussion

Acute endophthalmitis is a rare disease but one which may be associated with catastrophic complications, potentially leading to irreversible blindness. This condition is in upward surge, as ever greater incidence rates have been described.[13] Amongst other causes, this surge is mainly due to the increase in both intravitreal injection therapies, the most frequent procedure in ophthalmology practice in current times, and cataract surgery procedures throughout the world.[14,15]

Addressing this issue is of utmost importance to effectively reduce the impact of endophthalmitis, so prophylactic measures must be held at every intravitreal procedure. Safety protocols for IVI procedures must include the use of sterile gloves, sterile drapes and sterile eyelid specula (or equivalent equipment), as well as surgical-masks or, alternatively, a no-talking policy during procedures. Antiseptic application of topical povidone-iodine should prevail over topical antibiotics, as only povidone-iodine has shown to decrease the risk of endophthalmitis following IVIs and further avoids the financial costs and possible risk of increasing antibiotic resistance rates associated with topical antibiotic usage.[1,16-19] However, it is important to bear in mind povidone-iodine's toxicity to the corneal endothelial when in contact with the intraocular surface.[1,20]

For intraocular surgery procedures, topical povidone-iodine (or, alternatively, chlorhexidine) is also the standard of prophylactic care and should be applied to the cornea, conjunctival sac and periocular skin for a minimum of three minutes prior to surgery. It is also important to address the operating theatre's design, which should include standardized systems with separate clean and dirty circuits for all personnel and equipment involved in each surgery. Proper filtration of the operating theatre's airflow is required, and all operating theatres should be under positive pressure. Doors should be kept closed during procedures, except for transfers. All instruments for surgery should be sterile, single-use instruments should be preferred and sterilization protocols should be followed.[1]

Studying the treatment strategies of acute endophthalmitis cases in our population and assessing the visual outcomes obtained is key to enable specialists to provide the best possible approach to each and every patient.

This study represents the first national study of this kind, including a highly representative number of patients when compared to other single-center retrospective studies and including recent data which reflects modern developments in prophylactic protocols for

intraocular procedures and minimal incision VPP techniques for AEE's treatment.[21-26] These results were generally managed in a shorter studied time period when compared to the mentioned studies, fact which enhances the importance of this research and of the Integrated Responsibility Center for Ophthalmology of Centro Hospitalar e Universitário de Coimbra in the management of AEEs patients.

Current acute endophthalmitis treatment finds its foundations in the advent of intravitreal antibiotic injections, which took part in the 1970's following research conducted by Peyman *et al*.[27,28] Since then, the importance of antibiotic intraocular injections has been undisputed and is now widely used to achieve better treatment outcomes in acute endophthalmitis patients.[29,30]

The Endophthalmitis Vitrectomy Study (EVS) represents another important landmark in endophthalmitis treatment research. This major multicenter randomized clinical trial was published in 1995 and established a comparison between vitreous tapping and vitrectomy treatment strategies, recommending the second only when patients had LP only vision at presentation or worse.[16]

With the improvement in PPV technique over recent years, including the introduction of transconjunctival vitrectomy with ever smaller incision instrumentation, better cutting rates and duty cycle performance, enhanced endoillumination and wider-angle visualization techniques, this procedure has since been used more frequently than intraocular injections alone and has been recommended as "gold standard" by the European Society for Cataract & Refractive Surgeons (ESCRS).[1,31-33] In fact, an argument can be made that PPV may help to reduce infection load, clear vitreous opacification, and obtain better sampling for microbiology examination, bringing enhanced value to AEE treatment.[26,33]

Possible gains obtained by the generalization of PPV are still debatable, as recent studies which include modern PPV techniques struggle to confidently conclude better results were obtained when counting on this procedure. Some smaller single-center retrospective studies have concluded in favor of PPV general application as the primary treatment for AAEs (although with some limitations), but major studies failed to assert its superiority when compared to antibiotic IVI alone.[22,23,25,34,35] In the absence of major prospective studies including modern PPV techniques, retrospective studies like this one are of additional value to better understand its role in the treatment of endophthalmitis cases.

In our study, the final vision acuity results obtained were similar to the ones described in literature, and the improvement in visual acuity in both groups (treated with injections

alone or injections and PPV combined) was significant.[13,21,23,24] As previously described by Crosby N. J. *et al*., the fact that visual acuity results did not follow a normal distribution pattern can be seen as an advantage, as the use of non-parametric testing allows for the analysis of visual acuity gains to not be influenced by the absolute value of the LogMAR values assigned to the very low visual acuities, which are often inaccurate.[25]

The variation between pre- and post-treatment visual acuities was similar between the two groups, leading us to believe that injection + PPV treatment was not inferior to injection alone.

Both the need and timing for vitrectomy therapy are difficult to assess, but this treatment strategy is usually chosen in patients with more severe disease.[17] This may constitute a bias that can misguide the interpretation of our results, as poorer prognoses were to be expected from patients in which PPV was conducted. It is important to point out that prognosis factors related to endophthalmitis infections are vast, including advanced age, etiology, microbiological findings, time of diagnosis and treatment, but the most relevant factor has been shown to be the patient's visual acuity at time of presentation.[36]

As there was a significant difference in final visual acuity results when comparing the two groups of patients, with injection + PPV showing worse visual outcomes than injection alone, the similar variation in visual acuities between the two groups strengthens our view that PPV may have been applied in more severe cases, leading to similar visual gains in patients with worse prognosis that the ones treated without the use of PPV.

In our study, patients submitted to injection and PPV combined had higher presenting visual acuity values when compared to the patients submitted to injection alone. However, the comparison between the visual acuity results in each treatment group at time of presentation only manage a P value of 0.075, just shy of the significance level defined in this study's design. This fact can be related to the limiting number of participants included in this study and would most likely be overcome with the inclusion of a larger population, as made possible by multi-center studies.

This being said, the study failed to assert PPV's treatment superiority in patients' subgroups with worse presenting visual acuities, as visual acuity gains were similar to the ones obtained with injections alone. These results follow the findings described by most major studies in this field.

In our opinion, possible gains surpassing current recommendations related to the general use of VPP in the management of AEEs patients are to be determined my future larger studies, to which smaller single-center studies like this one may contribute.

No significant impact on visual acuity results was derived from data related to symptom onset or treatment initiation intervals. The same can be said for these variables' impact on the incidence of the two major complications (RD and evisceration).

It was not possible to study the impact on visual acuity results related to briefness in treatment initiation from the time of diagnosis because the great majority of patients started treatment on the day of presentation/diagnosis. However, literature indicates initiating treatment as soon as endophthalmitis is suspected is of extreme importance considering this disease's devastating consequences.[37,38] This is clearly exemplified by the results obtained by Januschowski K. *et al.* in a study published in 2020 in which all patients were treated within 6 hours of presentation time.[24]

When PPV procedure requisites are not available, antibiotic IVI injection is key and must be conducted even if a definitive microbiologic diagnosis is not possible. Intraocular injection procedures can take place almost universally at every hospital facility and should be conducted before the patient's rerouting to more centralized facilities like the Integrated Responsibility Center for Ophthalmology of Centro Hospitalar e Universitário de Coimbra.

Systemic antibiotics are recommended in the ESCRS guidelines and general practice dictates they should not be denied on an individual base. The pharmacokinetic principals behind the recommendation of systemic antibiotics lie on the fact that they can favor intraocular accumulation of intraocular injected antibiotics and expand their effect, since without systemic antibiotic administration almost complete removal from the intraocular space is to be expected after 24 hours.[39] On the other hand, blood-retinal barriers make it difficult for systemic antibiotics to penetrate into the tissues of the eye, and intraocular antibiotic levels are never comparable to the ones obtained when resorting to IVI. This may be the reason why systemic antibiotics are not generally supported by past endophthalmitis studies.[40]

In the EVS, the study design used different drugs systemically and intravitreally, thus not contributing towards maintaining effective antibiotic levels within the eye.[1,16] In our study, at least one antibiotic used systemically was the same as the ones used intravitreally in only 51.58% of patients submitted to systemic antibiotic therapy, failing to overcome this limitation of the EVS.

As the percentage of the patients included in this study who were given systemic antibiotics was just shy of 100%, we were not able to infer on its impact on the visual acuity gains.

Adjunctive subconjunctival and topical antibiotic administration are usually at discretion of the surgeon and have thus been used in fewer percentages of patients (15.66% and 91.57%, respectively), without showing significant improvement in their visual acuity results. The same was concluded in a previous study by Dave V. *et al.* regarding the use of topical antibiotics.[19]

All recorded cases of AEE were related to either intraocular procedures or penetrating trauma of the eye. Regarding cases following glaucoma surgery procedures, the bleb-related type of endophthalmitis usually take several months to develop following such procedures, with studies suggesting a mean symptom flare-up time of around 50 months. The 3 recorded cases included in our study that followed glaucoma surgery developed immediately after said procedure (under 6 weeks' time), so they were accounted as a result of the surgery itself (procedure-related) rather than bleb-related for the purposes of this study.

Major microorganisms may vary depending on geographical factors and endophthalmitis type, but our microbial findings concur with past reports as coagulase-negative Staphylococcus were the most common organism identified.[1,41-43] This was to be expected, as they are part of the flora typically found on the ocular surface.

Even tough Gram-positive microbes are most commonly associated with acute endophthalmitis, Gram-negative infections (in particular *Pseudomonas aeruginosa* infections) may occur and have been associated with poorer visual outcomes, reaffirming the need for a broad specter antibiotic coverage when treating this condition.[6,44] Antibiotic injection schemes and dosages followed in this study were in line with the ones recommended in previous studies and reviews, and the broad specter antibiotic coverage proved efficient as only one case required change in the intravitreal antibiotic plan, with injection of cefazolin following antibiotic resistance evidence in the antimicrobial susceptibility testing regarding an *Haemophilus influenzae* infection.[1,45]

Culture positivity rates were lower than the ones described in previous studies, usually located between 55 and 75%.[41,42,46,47] Our rates may have been artificially lower due an earlier treatment initiation (although this was not the case when comparing to every mentioned study), leaving less time for bacterial colonies to grow to detectable levels. In our study, culture positivity had a significant association with worse visual acuity results both before and after-treatment, probably due to the same principle (meaning cultures were easier to obtain in cases with a worse intraocular septic environment).

In an effort to increase culture sensitivity, a growth medium update was introduced in April 2021 which managed positivity rates of 37.04%. In fact, similar positivity rates were

presented in a study by Peng, K. L. *et al.* published in 2021, in which symptom onset and treatment initiation intervals were close to the ones registered in our study.[13]

The inclusion of molecular biology examination of the collected samples, using the polymerase chain reaction technic, is not currently available at the Ophthalmology Responsibility Center for this purpose but may further improve microbiological identification rates.

This study's limitations are related to the sample size, characteristic of single-center studies, and to its retrospective, nonrandomized study design. The data collection process is another limitation to be considered, since our study has missing data which may affect the quality of the results.

Despite these limitations, our study will add to current knowledge on acute endophthalmitis treatment. This is the first study to be completed on a national level, but similar studies are already underway in another four central hospital facilities. Therefore, a national sample that adequately reflects acute endophthalmitis cases in Portugal will be obtained. Since all five studies were constructed following the same methodology, they will allow us to evaluate the management and incidence of complications resulting from this condition in the whole country, through the development of a multicentric study.

Further studies, namely prospective, randomized controlled trials are warranted to continue the search for the best approach possible to improve outcomes for these patients.

Conclusion

Even though acute endophthalmitis represents a serious condition with possible catastrophic outcomes and poor visual prognosis, an improvement in visual acuity results was recorded in 71.08% of patients after treatment implementation. A median improvement value of -0.50 LogMAR (-1.68-0.00) was obtained when regarding all patients included in this study. Final vision acuity results were similar to previous literature descriptions, with a medium final vision acuity value of 0.80 LogMAR (0.20-2.28; SE: 20/125; LS: 45).

Despite including one of the highest numbers of patients in recent single-center studies of this kind, it was not possible to confidently demonstrate any superiority related to the general use of PPV in the management of acute endophthalmitis in our study.

Possible gains surpassing current recommendations related to the general use of PPV in the management of AEEs patients are to be determined my future larger studies, preferably prospective, randomized controlled trials which may continue the search for the best approach possible to improve outcomes for these patients.

In order to obtain a better understanding of this condition's pre-treatment, treatment-related and post-treatment factors, this study will be included in a large multicentric study which will adequately reflect acute endophthalmitis management in our country.

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