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Causative Pathogens of Endophthalmitis after Intravitreal Anti-VEGF Injection: An International Multicenter Study

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Keywords
Endophthalmitis · Intravitreal injection · Vascular endothelial growth factor

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Abstract
Purpose: The main objective of this study was to investigate the microbiological spectrum of endophthalmitis after anti-VEGF injections and to compare streptococcal with non-streptococcus-associated cases with regard to baseline characteristics and injection procedure. ***Methods:*** Retrospective,

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international multicenter study of patients with culture-positive endophthalmitis after intravitreal anti-VEGF injection at 17 different retina referral centers. ***Results:*** Eighty-three cases with 87 identified pathogens were included. Coagulase-negative staphylococci (59%) and viridans streptococci (15%) were the most frequent pathogens found. The use of postoperative antibiotics and performance of injections in an operating room setting significantly reduced the rate of streptococcus-induced endophthalmitis cases ($p = 0.01$ for both). ***Conclusion:*** We found a statistically significant lower rate of postinjectional local antibiotic therapy and operating room-based procedures among the streptococcus-induced cases compared to cases caused by other organisms.

Introduction

The use of intravitreal anti-vascular endothelial growth factor (VEGF) agents has revolutionized the management and visual prognosis for patients with several ocular diseases, mainly neovascular age-related macular degeneration [1, 2] and retinal vascular diseases such as retinal vein occlusion [3], diabetic macular edema [4], and proliferative diabetic retinopathy [5].

Acute-onset infectious endophthalmitis continues to be the most feared and significant complication of intravitreal injections, causing severe and potentially irreversible vision loss and is defined by an onset within 6 weeks after surgical intervention [6–8]. Each injection of anti-VEGF agents such as bevacizumab, ranibizumab, or aflibercept carries a small associated risk of endophthalmitis with a reported incidence of endophthalmitis after anti-VEGF injection between 0.01 and 0.32% [9–15]. Although the overall incidence of endophthalmitis is low, the probability is cumulative due to the recurrent, frequently monthly nature of the treatment regimen up to 1% [2].

To date, all multicenter studies investigating postinjection endophthalmitis have been nationwide or regional only, including medical centers from a few specific countries such as France, the UK, and the USA [6, 7, 10–12, 14]. In these publications, injection settings and postinjection recommendations were mostly similar within countries or local regions due to guidelines set by the national regulatory agencies. However, injection settings and postinjection recommendations differ significantly between settings in different countries around the world. To the best of our knowledge, comparative information regarding experience from different areas around the world using different injection settings is lacking, and it is unknown whether those have an impact on infectious pathogen distribution. Hence, the main purpose of this study was to describe the microbiological spectrum in cases of infectious endophthalmitis following anti-VEGF injections at 17 international retinal referral centers (Table 1) with different injection settings and postinjection regimens.

Table 1. Participating centers

1	Department of Ophthalmology, Charité – University Medicine Berlin, Germany
2	Department of Ophthalmology, University of Leipzig, Germany
3	Department of Ophthalmology, University Hospital Dijon, France
4	Service d'Ophtalmologie, Hôpital Lariboisière, AP-HP, Université Paris 7 – Sorbonne Paris Cité, Paris, France
5	St. Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, UK
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10	Ophthalmology Division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
11	Department of General Ophthalmology, Medical University in Lublin, Poland
12	Department of Ophthalmology, Pauls Stradins Clinical University Hospital, Riga, Latvia
13	Royal Victorian Eye and Ear Hospital, Melbourne, VIC, Australia
14	Department of Ophthalmology, Save Sight Institute, University of Sydney, Sydney, NSW, Australia
15	Retina Division, Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
16	Department of Ophthalmology, Faculty of Medicine, Rajavithi Hospital, Rangsit University, Bangkok, Thailand
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Table 2. Identified, included, and excluded cases among the study sites

Study site	Period of consecutive case selection	Total of identified endophthalmitis cases, *n*	Total of included cases, *n*	Excluded cases and reasons for exclusion, *n*	Method of pathogen identification
Berlin, Germany	01/2011 to 12/2016	23	15	8 (no pathogen identified)	Culture in 22 cases Culture + PCR in 1 case
Leipzig, Germany	01/2014 to 12/2016	5	3	2 (no pathogen identified)	Culture
Dijon, France	01/2011 to 02/2016	20	14	6 (no pathogen identified)	Culture + PCR in all cases
Paris, France	01/2011 to 12/2016	1	0	1 (no pathogen identified)	Culture
Liverpool, UK	01/2012 to 12/2016	12	7	5 (no pathogen identified)	Culture + PCR in all cases
Perugia, Italy	01/2011 to 12/2016	2	1	1 (no pathogen identified)	Culture
Coimbra, Portugal	01/2011 to 12/2016	5	1	4 (no pathogen identified)	Culture
Barcelona, Spain	01/2015 to 12/2016	1	0	1 (no pathogen identified)	Culture
Istanbul, Turkey	01/2016 to 12/2016	1	0	1 (no clear specification of identified pathogen)	Culture
Tel Aviv, Israel	01/2013 to 12/2016	15	11	4 (no pathogen identified)	Culture
Lublin, Poland	01/2015 to 12/2016	1	0	1 (no pathogen identified)	Culture
Riga, Latvia	01/2014 to 12/2016	3	0	3 (no pathogen identified)	Culture
Melbourne, Australia	01/2013 to 12/2016	25	14	11 (no pathogen identified)	Culture
Sydney, Australia	01/2013 to 12/2016	11	6	5 (no pathogen identified)	Culture
Chiang Mai, Thailand	01/2011 to 12/2015	7	1	6 (no pathogen identified)	Culture
Bangkok, Thailand	01/2016 to 12/2016	2	2	0	Culture
Buenos Aires, Argentina	01/2015 to 12/2016	8	8	0	Culture + PCR in all cases

Previous reports have indicated streptococcus-associated endophthalmitis to be associated with severer clinical outcomes than other pathogens [9, 10, 12]. However, little is known about the relation between baseline characteristics, injection settings and postinjection regimens, and streptococcal versus non-streptococcus-induced endophthalmitis cases. Thus, we secondarily aimed to describe a streptococcus-induced endophthalmitis cohort and compare baseline characteristics and injection characteristics in those cases to nonstreptococcal endophthalmitis cases.

Methods

Institutional review board approval was obtained through the individual institutional review boards at the participating institutes for a retrospective consecutive chart review. This was an international multicenter study including 17 centers (Table 1). Research adhered to the tenets of the Declaration of Helsinki.

Patient records from January 1, 2011, to December 31, 2016, were reviewed for cases of infectious endophthalmitis following intravitreal injections of anti-VEGF agents warranting tap and inject or pars plana vitrectomy (PPV).

Study Participants

Inclusion criteria were: (1) infectious endophthalmitis after intravitreal injection of an anti-VEGF agent within 6 weeks after injection; (2) vitreous sample acquired and antibiotic therapy administered by tap + inject or PPV; (3) identification of causative pathogen from vitreous sample. Exclusion criterion was any other intraocular procedure during the month preceding endophthalmitis.

Patients' charts were reviewed for demographic data, method of microbiological testing, identified causative pathogen from vitreous sample, previous intravitreal injections, previous use of local antibiotic therapy, indication for intravitreal injection, injected anti-VEGF drug, settings for intravitreal injection and injection procedure, use of routine postinjection antibiotic therapy, visual acuity (VA) prior, at endophthalmitis diagnosis and 1 month later, type of treatment (tap and inject vs. PPV), and medical treatment.

Statistical Analysis

Only cases with an identified pathogen were included in further statistical analysis. If two pathogens were identified from one vitreous sample, each pathogen was counted as a separate case. To control for the correlated nature of our data, we used a generalized estimating equations (GEE) procedure. Differences between streptococcal and nonstreptococcal cases were analyzed by a univariate GEE model by testing the following variables: (1) age, (2) VA at endophthalmitis diagnosis, (3) days of endophthalmitis onset (days between last injection and endophthalmitis diagnosis), (4) use of antibiotic therapy after injections, (5) presence of diabetes, (6) injection setting (office based vs. operating room), (7) use of local anesthesia, (8) application of local antibiotics immediately after injection, and (9) posttreatment antibiotic eye drops. A univariate GEE model for functional outcome after 1 month was run by testing the following predictors: (1) age, (2) VA prior to endophthalmitis, (3) VA at endophthalmitis diagnosis, (4) days of endophthalmitis onset, (5) underlying disease for which intravitreal therapy was conducted, (6) lens status, and (7) streptococcus-associated endophthalmitis. Predictors with a p value of less than

Table 3. Demographic, baseline, and outcome data (n = 83)

Mean age ± SD (n = 79), years	73±12
Sex (n = 83), n (%)	
Female	51 (61)
Male	32 (39)
Onset of endophthalmitis from injection (n = 77), days	4.0±3.6
VA prior to endophthalmitis (n = 40), logMAR	0.53±0.49
VA at endophthalmitis diagnosis (n = 76), logMAR	2.61±1.25
Geographic location of injection center, n (%)	
Europe	41 (49)
Australia	20 (24)
Asia	14 (17)
South America	8 (10)
Injected anti-VEGF drug, n (%)	
Ranibizumab	39 (47)
Aflibercept	22 (27)
Bevacizumab	17 (21)
Anti-VEGF drug unknown	5 (6)
Indication for IVI (n = 80), n (%)	
AMD	54 (68)
DME	19 (24)
CRAO/CRVO/BRVO	5 (6)
Myopic CNV	1 (1)
CSR-associated CNV	1 (1)
Conduction of previous injection(s) (n = 69), n (%)	60 (87)
Previous injections (n = 47), n	9.1±12.1
Use of previous postinjectional local antibiotic therapy at home (n = 56), n (%)	31 (55)
Lens status (n = 69), n (%)	
Phakic	44 (64)
Pseudophakic	25 (36)
Diabetic patient (n = 72), n (%)	28 (39)
Injection setting (n = 78), n (%)	
Operating room	41 (49)
Office	37 (45)
Use of facial mask (n = 58), n (%)	57 (98)
Use of sterile gloves (n = 65), n (%)	65 (100)
Topical anesthesia (n = 47), n (%)	
Drops only	37 (79)
Gel (±drops)	10 (21)
Application of antibiotics immediately after IVI (n = 46), n (%)	40 (87)
Posttreatment antibiotic eye drops (n = 54), n (%)	22 (41)
VA at 1 month (n = 52), logMAR	1.15±0.94

SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor; IVI, intravitreal injection; AMD, age-related macular degeneration; DME, diabetic macular edema; CRAO, central retinal artery occlusion; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; CNV, choroidal neovascularization; CSR, central serous retinopathy.

0.20 in the univariate analysis were included in a multivariate GEE model. In the final multivariate model, a backward selection procedure was carried out, retaining only those predictors with $p < 0.05$. To control for multiple testing, a Bonferroni correction was carried out. Values are presented as means ± standard deviation. Statistical analysis was performed with SPSS Statistics 22 (IBM, Armonk, NY, USA).

Results

A total of 17 study sites participated in this study, reporting 142 cases of endophthalmitis after anti-VEGF injection in total. Details are displayed in Table 2. In 58 cases (40.8%) no pathogen was identified from the vitreous sample, and thus they were not included in further

analysis. In 1 case (0.7%) the identified pathogen was not properly specified (microbiology lab results: gram-positive cocci) and thus excluded. All study sites performed a culture-based pathogen identification. In 4 study sites pathogen detection was additionally performed using polymerase chain reaction.

A total of 83 cases of culture-positive endophthalmitis (58.4%) were included. Characteristics of culture-positive cases are detailed in Table 3. There were no cases of cluster endophthalmitis.

Microbiological Spectrum

Eighty-seven pathogens were identified from the vitreous samples (in 4 patients 2 different pathogens were identified, Table 4). In all 4 cases with 2 identified pathogens, both pathogens were nonstreptococcal. The most frequent pathogens were coagulase-negative staphylococci (59%), viridans streptococci (15%) and *Staphylococcus aureus* (12%). Ten nonstreptococcal and nonstaphylococcal pathogens were identified (Table 4).

Table 4. Identified pathogens (n = 87)

Staphylococcaceae, *n* (%)	**62 (71)**
Coagulase-negative staphylococci	52 (60)
Staphylococcus epidermidis	43 (49)
Not further specified	4 (5)
Staphylococcus lugdunensis	2 (2)
Staphylococcus capitis	2 (2)
Staphylococcus warneri	1 (1)
Staphylococcus aureus	10 (12)
Streptococcaceae, *n* (%)	**15 (17)**
Viridans streptococci	13 (15)
Not further specified	8 (9)
Streptococcus mitis	2 (2)
Streptococcus anginosus	1 (1)
Streptococcus salivarius	1 (1)
Streptococcus oralis	1 (1)
Streptococcus pneumoniae	1 (1)
Granulicatella adiacens	1 (1)
Others, *n* (%)	**10 (12)**
Propionibacterium acnes	3 (3)
Enterococcus faecalis	2 (2)
Haemophilus influenzae	1 (1)
Neisseria macacae	1 (1)
Paenibacillus spp.	1 (1)
Klebsiella spp.	1 (1)
Pseudomonas spp.	1 (1)

Comparison of Baseline Characteristics and Injection Procedure

For further analyses, all cases were categorized by causative pathogen: nonstreptococcal (Staphylococcaceae and others) or Streptococcaceae. Baseline characteristics and data on injection and postinjection procedures are displayed in Table 5. In all cases, pre-injection betadine sterilization of the fornix was performed.

Cases of streptococcus-induced endophthalmitis had a statistically significant lower rate of postinjection local antibiotic use preceding the endophthalmitis compared to the nonstreptococcal group (p = 0.01). Data about posttreatment antibiotic eye drops were provided for 56 cases (64.3%). In 34 cases from 4 different centers (Melbourne n = 15, Tel Aviv n = 10, Liverpool n = 8, Sydney n = 1), postinjection antibiotic therapy after the last injection was denied and in 22 cases from 6 different centers confirmed. Regimens of antibiotic therapy differed among the centers. Used drugs were moxifloxacin (40.9%; 9 cases: Buenos Aires n = 8; Perugia n = 1), azithromycin (36.4%; 8 cases: Dijon n = 8), tobramycin (13.6%, 3 cases: Bangkok n = 2, Chiang Mai n = 1), and ofloxacin (9.1%, 2 cases: Dijon n = 1, Coimbra n = 1).

After univariate analysis, the following variables were included in the multivariate analysis: injection setting and continued use of posttreatment antibiotic eye drops. Both variables were identified as significant in multivariate analysis. The use of postoperative antibiotics and performance of injections in an operating room setting significantly reduced the rate of streptococcus-induced endophthalmitis cases (p = 0.01 for both).

Treatment

Initial treatment was by tap and intravitreal antibiotic injection in 49 patients (59%). Twenty-one of these patients (43%) did not require any further surgical treatment, 12 patients (25%) underwent at least one further tap and inject procedure, and in 16 patients (33%) secondary PPV was performed. Thirty-four patients (41%) were treated by primary PPV. Eighteen of these patients (53%) did not require any additional surgical procedure, 12 patients (35%) underwent a second PPV and in 3 patients (9%) a secondary tap and inject procedure was performed. In 1 patient (3%) secondary enucleation was conducted.

All patients received at least one intravitreal antibiotic injection. The mean number of intravitreal antibiotic injections was 1.8 ± 0.8 (range: 1–4 injections). The intravitreal antibiotic therapies used were: vancomycin plus ceftazidime in 72 patients (87%), vancomycin plus ceftazidime and dexamethasone in 10 patients (12%), and vancomycin plus amikacin in 1 patient (1%). Sixty-two pa-

Table 5. Demographic, baseline, and outcome data stratified for causative pathogen, univariate analysis

	Nonstreptococcal		Streptococcal (n = 15)	p value[1]
	staphylococcal (n = 62)	others (n = 10)		
Age, years	73±13 (n = 60)	77±13 (n = 10)	74±8 (n = 13)	0.88
VA prior to endophthalmitis onset (mean ± SD, range), logMAR	0.56±0.53 (0.1 to 3.0) (n = 31)	0.37±0.36 (–0.1 to 0.8) (n = 6)	0.47±0.34 (0.2 to 1.0) (n = 5)	0.74
VA at endophthalmitis diagnosis, logMAR	2.50±1.18 (n = 59)	3.30±1.48 (n = 9)	2.76±1.18 (n = 11)	0.66
<1.0 logMAR, n (%)	9 (15)	1 (11)	2 (18)	
1.0–1.9 logMAR, n (%)	7 (12)	0 (0)	0 (0)	
Counting fingers, n (%)	7 (12)	1 (11)	0 (0)	
Hand motion, n (%)	31 (53)	4 (44)	8 (73)	
Light perception, n (%)	5 (8)	3 (33)	1 (9)	
Endophthalmitis onset, days	4.3±4.9 (n = 56)	5.9±8.1 (n = 10)	3.0±2.6 (n = 15)	0.40
Injected anti-VEGF drug	(n = 58)	(n = 10)	(n = 14)	0.16
Ranibizumab (n = 42)	31 (53)	6 (60)	5 (36)	
Aflibercept (n = 22)	18 (31)	1 (10)	3 (21)	
Bevacizumab (n = 18)	9 (16)	3 (30)	6 (43)	
Indication for IVI	(n = 60)	(n = 10)	(n = 14)	0.45
AMD (n = 57)	38 (63)	8 (80)	11 (79)	
DME (n = 19)	16 (27)	1 (10)	2 (14)	
Others (n = 8)	6 (10)	1 (10)	1 (7)	
Previous use of local antibiotic therapy	(n = 41)	(n = 7)	(n = 8)	0.02
Yes (n = 31)	30 (73)	1 (14)	0 (0)	
No (n = 25)	11 (27)	6 (86)	8 (100)	
Diabetic patient	(n = 53)	(n = 6)	(n = 15)	0.95
Yes (n = 28)	21 (40)	1 (16)	6 (40)	
No (n = 46)	32 (60)	5 (83)	9 (60)	
Lens status	(n = 51)	(n = 8)	(n = 12)	0.37
Phakic (n = 45)	33 (65)	3 (38)	9 (75)	
Pseudophakic (n = 26)	18 (35)	5 (63)	3 (25)	
Injection setting	(n = 58)	(n = 8)	(n = 15)	0.09
Operation room (n = 44)	33 (57)	6 (75)	5 (33)	
Office (n = 37)	25 (43)	2 (25)	10 (66)	
Local anesthesia	(n = 34)	(n = 5)	(n = 9)	0.43
Drops only (n = 38)	25 (73)	5 (100)	8 (89)	
Gel (±drops) (n = 10)	9 (26)	0 (0)	1 (11)	
Application of antibiotics immediately after IVI	(n = 32)	(n = 5)	(n = 10)	0.46
Yes (n = 41)	28 (88)	5 (100)	8 (80)	
No (n = 6)	4 (12)	0 (0)	2 (20)	
Posttreatment antibiotic eye drops	(n = 37)	(n = 7)	(n = 13)	0.01
Yes (n = 22)	21 (57)	1 (14)	0 (0)	
No (n = 35)	16 (43)	6 (86)	13 (100)	
VA after 1 month, logMAR	0.89±0.71 (n = 35)	1.08±1.14 (n = 6)	2.04±1.09 (n = 10)	0.001
<1.0 logMAR, n (%)	23 (66)	4 (67)	2 (20)	
1.0–1.9 logMAR, n (%)	8 (23)	0 (0)	3(30)	
Counting fingers, n (%)	2 (6)	1 (17)	0 (0)	
Hand motion, n (%)	2 (6)	1 (17)	5 (50)	
Light perception, n (%)	0 (0)	0 (0)	0 (0)	

Results are indicated as means ± SD or numbers with percentages in parentheses, calculated for the number of organisms in each group. In the second results part, total numbers and percentages per pathogen group are indicated. SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor; IVI, intravitreal injection; AMD, age-related macular degeneration; DME, diabetic macular edema. [1] p value for difference between nonstreptococcal and streptococcal.

tients (75%) received additional systemic antibiotic therapy. The most frequently used systemic antibiotics were: vancomycin plus ceftazidime intravenously (32%), ciprofloxacin orally (27%), moxifloxacin orally (16%), and imipenem plus cilastatin intravenously combined with oral levofloxacin (16%).

Baseline and Outcome Measures Stratified for Visual Outcome

VA after 1 month was 0.92 ± 0.77 logMAR in nonstreptococcal cases, versus 2.04 ± 1.09 logMAR in streptococcus-associated cases. After univariate analysis, the following predictors for visual outcome after 1 month were included in the multivariate analysis: VA prior to endophthalmitis, days of endophthalmitis onset, and streptococcus association. Multivariate analysis revealed VA prior to endophthalmitis being predictive for visual outcome after 1 month ($p = 0.04$, unstandardized coefficient: 0.65).

Discussion

To our best knowledge, this multicenter study represents the largest comprehensive report about identified causative pathogens for endophthalmitis after anti-VEGF injections. The majority of cases of culture-positive postinjection endophthalmitis were caused by staphylococci (71%), followed by streptococci (17%). Nonstaphylococcal and nonstreptococcal pathogens accounted for 12% of all endophthalmitis cases in our study. This proportion is in agreement with previous reports of nationwide studies [9, 11–13, 16, 17]. In contrast to other studies, the present one included 17 international retina referral centers in Europe, Australia, Asia, and South America. In 4 cases, 2 pathogens were identified from vitreous samples, all of them nonstreptococcal. It needs to be considered that this might be caused by contamination.

Streptococcus-induced endophthalmitis has previously been shown to be associated with worse outcome compared to nonstreptococcal cases [10, 12, 16]. Therefore, the second objective of this study was to describe the streptococcus-induced endophthalmitis cohort and compare baseline characteristics and injection procedure to nonstreptococcal endophthalmitis cases.

Our results confirm previous reports, showing that cases of streptococcus-induced endophthalmitis are characterized by a worse functional outcome [10, 12, 16]. Our study revealed a higher rate of office-based procedures in the streptococcus-associated group. Streptococcal isolates are approximately 3 times more frequent in postinjection cases, compared to endophthalmitis after cataract surgery [9, 10, 16]. It is assumed that this may be caused by the higher risk of iatrogenic infection due to oral flora during office-based procedures compared to those performed under sterile conditions of the operating room [10]. Previous studies on the effect on agar plate contamination revealed a significant increase in colony counts, with a predominance of streptococci, when not wearing a face mask and talking [18–20]. In this retrospective study we did not have the opportunity to evaluate for "no-talking" policy during the anti-VEGF injection which caused the endophthalmitis. Since the use of a facial mask was denied only in 1 case, we were also not able to clarify whether lack of a facial mask may be a predictor of streptococcus-caused endophthalmitis. Hence, further studies are necessary to reveal the causative relation between office-based procedures and the increased proportion of streptococcus-associated cases.

Besides procedure setting, use of posttreatment antibiotic eye drops differed significantly among the pathogen groups. We found a statistically significantly higher rate of streptococcus-associated cases when patients were not treated by postoperative topical antibiotic therapy. Previous reports [21–26] showed that the administration of local antibiotics does not reduce the incidence of endophthalmitis after anti-VEGF injections. Our findings suggest that use of local postinjection antibiotic therapy may influence the distribution of causative pathogens, favoring less severe non-streptococcus-associated cases. The use of routine postinjection antibiotics, however, needs to be assessed in the context of chronic diseases needing ongoing anti-VEGF treatments. Previous studies have shown an increased rate of antibiotic-resistant coagulase-negative *Staphylococcus* strains in the conjunctiva of patients receiving multiple courses of local antibiotic therapy [27–29]. Furthermore, there are reports of an increased rate of endophthalmitis cases caused by antibiotic-resistant coagulase-negative *Staphylococcus* over the last two decades [30, 31]. It is suspected that antibiotic-resistant strains cause more inflammation and destruction of the infected retina than nonresistant pathogens, as shown in an animal model [32]. Recently, Reibaldi et al. [33] even reported a higher risk of endophthalmitis with the use of topical antibiotic after intravitreal injection of anti-VEGF. Therefore, the role of routine antibiotic therapy after intravitreal injections remains controversial. Even more, age, presence of diabetes, form of local anesthesia and single application of local antibiotics immediately after injection did not differ significantly between both groups.

This was a retrospective chart review and was limited to the available evaluation and documentation. Thus, information whether ranibizumab was used in a prefilled syringe or from a vial was not provided and may have changed during the study period. Furthermore, the vitreoretinal interface was not evaluated as a prognostic factor, since preoperative optical coherence tomography scans were not available. Differences in endophthalmitis management were not included in the statistical analysis and could have influenced the visual outcome. Although this is the largest comprehensive study of culture-positive postinjection endophthalmitis cases, it is a rare complication and the small size may have been underpowered to detect minor effects. Cases in which the injection procedure was carried out at an external center were also included in this study; thus, we were not able to provide information on the incidence of endophthalmitis cases among the study sites, among different injection procedures, or among the used anti-VEGF agents. Some geographic areas were underrepresented (Asia, South America) or not present (North America) in our study. Furthermore, the culture positivity differed among the centers, which needs to be taken into consideration.

In summary, our study is the first to describe the distribution of endophthalmitis-inducing pathogens after anti-VEGF injections at 17 international recruitments centers. We found that streptococcus-induced endophthalmitis cases were more common when the patient did not receive postinjectional local antibiotic therapy and the injection was performed as an office-based procedure. In agreement with previous studies, our investigation found that streptococcus-associated endophthalmitis was associated with worse functional outcome.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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