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Filtering-Associated Endophthalmitis after Trabeculectomy or Tube-Shunt Implant

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Purpose: To determine the rate, clinical features, and outcomes of filtering-associated endophthalmitis in eyes that underwent trabeculectomy or tube-shunt implantation.

Design: Retrospective database study with selective chart review.

Participants: Eyes that underwent incisional glaucoma surgery at our institution between January 1, 2012, and December 31, 2019.

Methods: An electronic medical record database was used to identify all eyes that underwent trabeculectomy or tube-shunt implantation during the study period. Date of surgery, date of last ophthalmology clinic visit, and filtering-associated endophthalmitis diagnoses were obtained and used to perform a Kaplan-Meier analysis. The log-rank test was used to compare rates of filtering-associated endophthalmitis after trabeculectomy and tube-shunt implantation. Microbiology, management, and clinical outcomes data from patients with filtering-associated endophthalmitis were also collected and analyzed.

Main Outcome Measures: Cumulative risk of filtering-associated endophthalmitis as determined by Kaplan-Meier analysis. Visual acuity improvement to within 2 lines of baseline at 3 months of follow-up and globe salvage at last available follow-up in eyes with filtering-associated endophthalmitis.

Results: Kaplan-Meier analysis of 1582 eyes that underwent incisional glaucoma surgery yielded a 5-year cumulative incidence for filtering-associated endophthalmitis of 1.32%. No statistically significant differences were found between rate of endophthalmitis after trabeculectomy or tube-shunt implantation ($P = 0.761$, log-rank test). Seven of 16 cases (43.8%) of filtering-associated endophthalmitis showed positive culture results from either a vitreous sample or explanted tube shunt. Recovery of vision to within 2 lines of pre-endophthalmitis baseline was achieved in 53% of patients at 3 months of follow-up. Rate of globe salvage was 100% at last available follow-up.

Conclusions: Risk of filtering-associated endophthalmitis is persistent and relatively constant for at least 5 years after incisional glaucoma surgery. The overall prognosis of filtering-associated endophthalmitis remains poor; however, good visual and anatomic outcomes can be achieved in some patients with prompt intervention. *Ophthalmology Retina 2021;5:279-284 © 2020 by the American Academy of Ophthalmology*

Endophthalmitis related to incisional glaucoma surgery or filtering-associated endophthalmitis is a vision-threatening complication that is notoriously difficult to treat. The 2 major categories of incisional glaucoma surgery are trabeculectomy and tube-shunt implantation. Both create a permanent pathway between the anterior chamber and subconjunctival space, which elevates the lifelong risk of intraocular bacterial spread.

Vitreous inflammation in the setting of filtering-associated infection is the key finding that differentiates endophthalmitis from localized blebitis and has important management and prognostic implications. Compared with endophthalmitis occurring after other types of intraocular surgery, filtering-associated endophthalmitis has worse visual and anatomic outcomes, with rates of no light perception (NLP) vision as high as 23% to 35%.[1–4] Reported rates of endophthalmitis after trabeculectomy vary widely, ranging from 0.2% to 13%, with the highest rates seen with inferior trabeculectomies.[5–8] Tube-shunt implantations carry the additional risks of erosion and biofilm formation; the rate of associated endophthalmitis in the current literature ranges from 0.8% to 3%.[9–12] In this study, we aimed to describe the rate, clinical features, and outcomes of filtering-associated endophthalmitis in patients who underwent trabeculectomy or tube-shunt implantation at our institution.

Methods

This retrospective study conducted at a single, tertiary referral center was approved by the institutional review board of Oregon Health & Science University and adhered to the tenets of the Declaration of Helsinki. We used an electronic medical record (EMR) database search of Current Procedural Terminology codes to identify all eyes that underwent incisional glaucoma surgery at our institution between January 1, 2012, and December 31, 2019 (trabeculectomy: 66170 [fistulization of sclera for glaucoma, trabeculectomy ab externo in absence of

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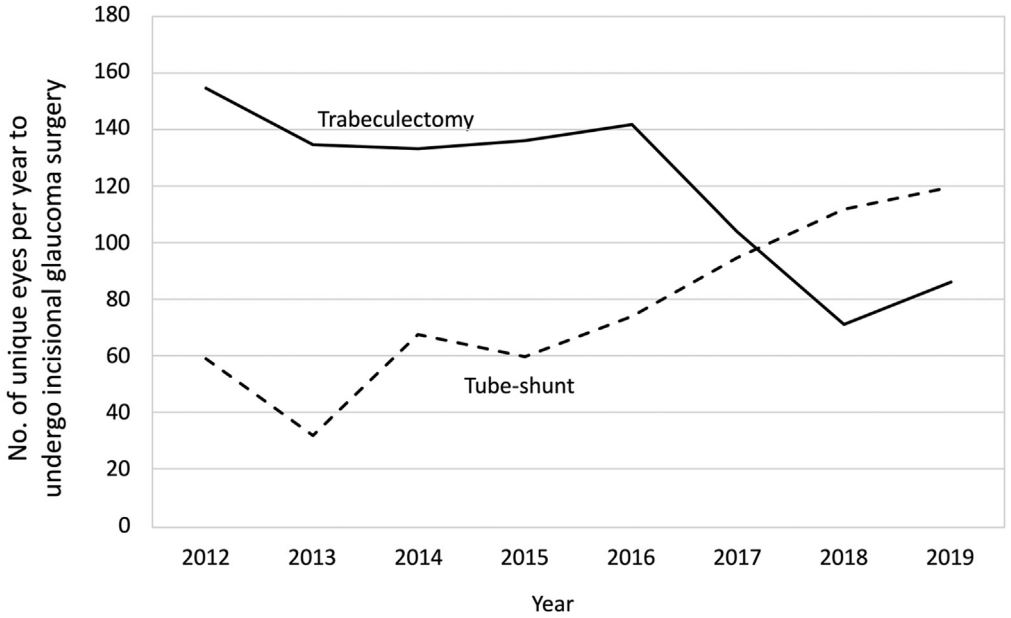

Figure 1. Line graph showing the number of unique eyes per year to undergo incisional glaucoma surgery.

previous surgery] and 66172 [fistulization of sclera for glaucoma, trabeculectomy ab externo with scarring from previous ocular surgery or trauma]; tube-shunt implantation: 66180 [aqueous shunt to extraocular equatorial plate reservoir, external approach, with graft] and 66179 [aqueous shunt to extraocular equatorial plate reservoir, external approach, without graft]). The dates of surgery and last ophthalmology clinic visit were obtained for each individual using the same EMR database. For the purpose of this analysis, surgery on both eyes of 1 individual was considered to be 2 independent events. For individual eyes that underwent multiple incisional glaucoma surgeries, only the earliest surgery within the study period was included.

Further query with relevant International Classification of Diseases (ICD) codes was performed to identify patients who underwent incisional glaucoma surgery during the study period and had a diagnosis of endophthalmitis (ICD Ninth Edition codes: 379.63 [bleb-associated endophthalmitis], 360.00 [purulent endophthalmitis, unspecified], 360.01 [acute endophthalmitis], 360.03 [chronic endophthalmitis], and 360.19 [other endophthalmitis]; ICD Tenth Edition codes: H44.001 [unspecified purulent endophthalmitis, right eye], H44.002 [unspecified purulent endophthalmitis, left eye], H44.003 [unspecified purulent endophthalmitis, bilateral], H44.009 [unspecified purulent endophthalmitis, unspecified eye], H44.19 [other endophthalmitis], and H59.43 [inflammation (infection) of postprocedural bleb, stage 3]). An individual chart review was performed of patients with an endophthalmitis diagnosis code, and these were excluded if (1) no evidence of vitritis was found on examination by a retinal specialist or (2) endophthalmitis was attributed to a factor other than a filtering bleb or tube shunt (i.e., intravitreal injection, corneal ulcer, or endogenous spread).

Kaplan-Meier analysis was performed and graphed as hazard plots to assess the rate of endophthalmitis related to incisional glaucoma surgery. Eyes were censored at date of last ophthalmology clinic visit if they had no filtering-associated endophthalmitis diagnosis. The 5-year cumulative incidence was determined using Kaplan-Meier analysis. A log-rank test was performed to compare the endophthalmitis rates after trabeculectomy and tube-shunt surgeries. A P value of less than 0.05 was considered statistically significant.

A second search was performed to identify cases of filtering-associated endophthalmitis in patients who had undergone surgery before 2012 or at an outside institution; these additional cases were included in microbiology, treatment, and outcome analysis but not in the Kaplan-Meier analysis. Data recorded included age, gender, type of glaucoma surgery, time from glaucoma surgery to endophthalmitis diagnosis, presence of bleb leak or tube-shunt exposure, microbial culture results, and clinical management, as well as vision and globe status at 3 months after diagnosis and at the last available follow-up visit. Descriptive statistics, chi-square test results, and Student t test results were reported. Kaplan-Meier and all statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY).

Results

Kaplan-Meier Analysis and 5-Year Cumulative Incidence

A total of 1582 eyes underwent incisional glaucoma surgery at our institution between January 1, 2012, and December 31, 2019. During the study period, 60.8% eyes underwent a trabeculectomy and 39.2% eyes underwent a tube-shunt implantation as the first or only incisional glaucoma surgery. As shown in Figure 1, the yearly proportion of trabeculectomy surgeries fell throughout the study period. Ten cases of endophthalmitis attributed to incisional glaucoma surgeries performed at our institution during the study period were identified. Kaplan-Meier analysis of filtering-associated endophthalmitis after incisional glaucoma surgery is shown in Figure 2 and yielded a 5-year cumulative incidence of 1.32%. No statistically significant difference was found in rate of filtering-associated endophthalmitis in eyes that underwent trabeculectomy compared with tube-shunt implantation (Fig 2B; $P = 0.761$, log-rank test).

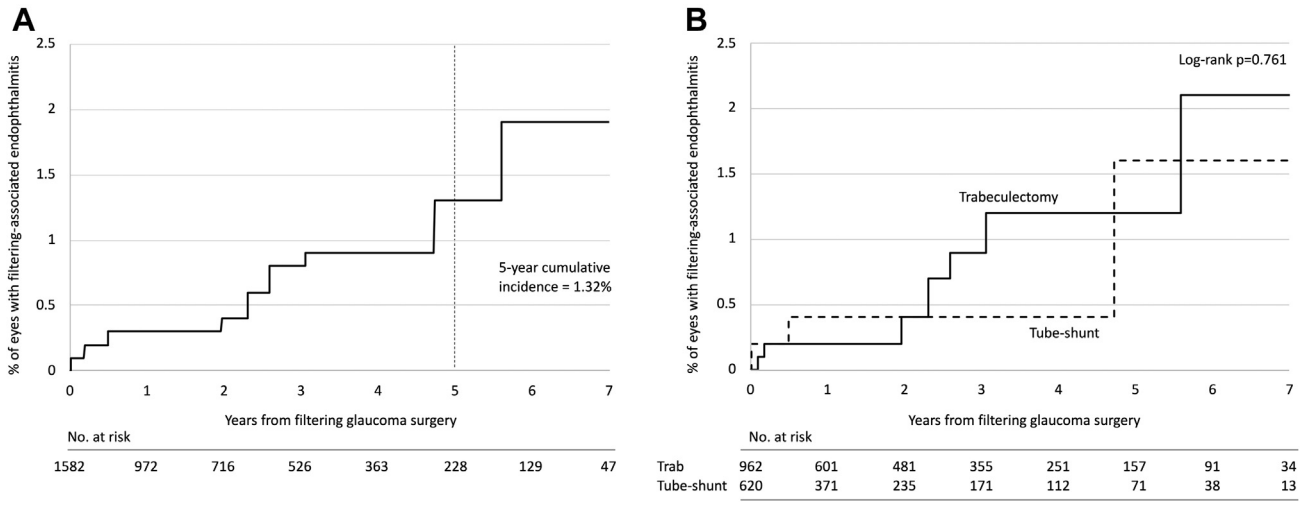

Figure 2. Hazard plot of Kaplan-Meier analysis for filtering-associated endophthalmitis (**A**) after any incisional glaucoma surgery or (**B**) stratified by trabeculectomy or tube-shunt implantation.

Microbiology Analysis, Management, and Outcomes

In a separate analysis, an additional 6 patients with filtering-associated endophthalmitis treated at our institution who had undergone incisional glaucoma surgery outside of the 2012-to-2019 study period or at an outside institution were included, yielding a total of 16 patients. The average age at diagnosis was 71.6 ± 12.3 years, and 25% of patients were women (Table 1). Twelve of 16 cases of endophthalmitis (75%) were associated with trabeculectomy and 4 of 16 cases of endophthalmitis (25%) were associated with tube-shunt implantation. The median time from incisional glaucoma surgery to diagnosis of endophthalmitis was 44.7 months (range, 1.8–317.5 months) for trabeculectomy and 43.2 months (range, 0.2–87.4 months) for tube-shunt implantation ($P = 0.191$). For trabeculectomy-associated cases, 2 eyes (16.7%) were treated for isolated blebitis before diagnosis of endophthalmitis and 6 eyes (50%) showed a bleb leak with positive Seidel test diagnosed at a median of 1 day (range, 0–48 days) before endophthalmitis diagnosis. For tube-shunt–associated cases, 3 eyes (75%) demonstrated conjunctival erosion and tube exposure at the time of diagnosis. All 16 eyes had undergone a superiorly located initial filtering surgery.

Table 1. Demographic Characteristics and Microbial Culture Results in Eyes with Filtering-Associated Endophthalmitis (n = 16)

Features	Data
Age (yrs), mean ± SD	71.6 ± 12.3
Female gender, no. (%)	4 (25)
Trabeculectomy (%)	75
Tube-shunt implantation (%)	25
Months from incisional glaucoma surgery to endophthalmitis diagnosis	
Median	44.7
Range	0.2–317.5
By type of surgery	
Trabeculectomy	
Median	44.7
Range	1.8–317.5
Tube-shunt implantation	
Median	43.2
Range	0.2–87.4
P value	0.191
Culture-positive results (%)	43.8
Cultured organisms, no.	
Streptococcus mitis	2
Haemophilus influenzae	1
Moraxella species	1
Pseudomonas aeruginosa	1
Staphylococcus epidermidis	1
Coagulase-negative Staphylococcus	1

SD = standard deviation.

Visual acuity at the time of diagnosis of endophthalmitis ranged from 20/30 to light perception. Vision was 20/40 or better in 6.3% of patients, 20/50 to 20/400 in 12.5% of patients, counting fingers or hand movements (HM) in 43.8% of patients, and light perception in 37.5% of patients. Mean follow-up from time of diagnosis was 28.8 ± 29.4 months, and follow-up visual acuity at 3 months after diagnosis was available in 93.8% of cases. All patients were treated with either prompt (within 24 hours) pars plana vitrectomy (PPV) with vitreous sampling and intravitreal antibiotics or vitreous sampling and antibiotic injection alone (tap and inject). Prompt PPV was performed in 70% of patients who demonstrated HM or worse vision and in none of the patients who demonstrated counting fingers or better vision. Two patients, both of whom demonstrated HM or worse vision at presentation, were treated initially with tap and inject then subsequently underwent PPV 3 to 5 days after initial diagnosis. All 4 patients with tube-shunt–associated endophthalmitis underwent tube-shunt explantation.

Bacterial culture from vitreous aspirate or explanted tube-shunt implant showed positive results in 7 of 16 patients (43.8%). Isolated organisms consisted of gram-positive bacteria (n = 4 [57.1%]; including *Streptococcus mitis* and *Staphylococcus* species) and

Table 2. Management and Outcome Data in Filtering-Associated Endophthalmitis Stratified by Presenting Visual Acuity

	Presenting Vision		
	Hand Movements or Worse (n = 10)	*Counting Fingers or Better (n = 6)*	**P Value**
Age (yrs)	68.7	76.3	0.196
Months from incisional glaucoma surgery to endophthalmitis diagnosis	75.3	102.6	0.659
Underwent PPV (%)	90	0	0.000
Improvement in visual acuity to within 2 lines of baseline visual acuity (%)			
3 mos	44.4	66.7	0.398
Last follow-up	44.4	50.0	0.833
Globe salvage (%)	100	100	

PPV = pars plana vitrectomy.
Follow-up visual acuity and globe salvage data available from 15 of 16 eyes.

gram-negative bacteria (n = 3 [42.9%]; including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Moraxella* species).

Visual acuity at 3 months after treatment ranged from 20/30 to HM. Vision was 20/40 or better in 33% of patients, 20/50 to 20/400 in 47% of patients, and counting fingers or worse in 20% of patients. Improvement in visual acuity to within 2 lines of pre-endophthalmitis baseline was seen in 53.3% of patients at the 3-month time point (Table 2). No eyes had been enucleated or had NLP vision at 3 months or last available follow-up.

Discussion

Filtering-associated endophthalmitis is a severe, vision-threatening complication of trabeculectomy or tube-shunt implantation. Because of the extraocular aqueous reservoir protected only by conjunctival tissue and the permanent tract from the subconjunctival space to the anterior chamber created by these surgeries, endophthalmitis can develop at any time.

A wide range of incidence rates have been reported for the development of filtering-associated endophthalmitis.[5–12] This variability is likely multifactorial and influenced by surgical technique, patient population, study methods, and duration of follow-up. Because the risk of endophthalmitis persists indefinitely but may also change to some degree based on time from surgery, a Kaplan-Meier analysis provides a more complete evaluation of risk than a single yearly or cumulative incidence value. In the present study, Kaplan-Meier plots demonstrated a relatively steady slope, suggesting that endophthalmitis risk persisted through at least the first 5 years after surgery. To compare our study with others that reported incidence values, we used our Kaplan-Meier analysis to determine the 5-year cumulative incidence of filtering-associated endophthalmitis, which was 1.32% for all surgeries. This value fell within the range of previously reported rates and was particularly close to the 5-year cumulative incidence rate reported in an analysis using a large United States commercial health insurance claims-based database.[13] A major contributor to the decrease in the rate of filtering-associated endophthalmitis over the past few decades is likely the shift in surgical practice away from inferior bleb placement, which was identified as one of the greatest risk factors for infection.[6]

Previous studies have identified an aqueous leak through a focal conjunctival defect as a significant risk factor for the development of bleb-related infections.[14] In the present study, conjunctival breakdown in the area of prior glaucoma surgery was commonly seen at the time of endophthalmitis diagnosis. A bleb leak was present in 50% of trabeculectomy-associated endophthalmitis cases and conjunctival erosion with tube exposure was present in 75% of tube-shunt–associated endophthalmitis cases. The use of intraoperative antimetabolites, such as 5-fluorouracil and mitomycin C, has also been identified as a risk factor for filtering-associated endophthalmitis.[8,15] These agents increase the success of filtering surgery by reducing scar tissue formation but can also create thinner, avascular blebs more susceptible to infection. Reassuringly, rates of endophthalmitis associated with filtering surgeries using antimetabolite agents have declined more recently, which may be attributed to better surgeon familiarity with antimetabolite use and evolving surgical technique.[16] Because the intraoperative use of antimetabolite agents is not coded for separately at the time of filtering surgery, we were unable to stratify by antimetabolite use in our dataset. However, it is worth noting that intraoperative use of mitomycin C is standard practice among most of the glaucoma surgeons at our institution.

Compared with cataract surgery, endophthalmitis after filtering surgery is relatively rare because of lower surgical volume and portends a worse visual prognosis. Management of endophthalmitis after cataract surgery is guided by the Endophthalmitis Vitrectomy Study; however, the extent to which these guidelines can be applied to filtering-associated endophthalmitis is unclear because multiple differences in these clinical entities exist.[17] More virulent bacterial pathogens, particularly Streptococcal species, are more common in endophthalmitis occurring after filtering surgery than after cataract surgery.[3,4,18] The presence of a subconjunctival aqueous reservoir and, in the case of tube-shunt implants, an intraocular foreign body may make clearing infection more difficult. As such, some vitreoretinal surgeons have a lower threshold for prompt surgical

intervention in these patients. In our series, most patients with HM or worse vision underwent PPV: 70% within 24 hours and 90% within 5 days. In general, visual outcomes after filtering-associated endophthalmitis are poor. Rates of NLP vision or enucleation are as high as 23% to 35% in some reports, although many of these series are limited to trabeculectomy only.[1–4] Compared with other series, our patients showed better presenting and final visual acuities. No cases of NLP vision or enucleation occurred in our series, and 53.3% of patients achieved visual acuity improvement to within 2 lines of baseline at the 3-month follow-up. Many potential factors may have contributed to better visual acuity and anatomic outcomes, including lower referral threshold, earlier intervention, or less virulent pathogens; however, the present study was not powered to test these factors adequately. In the case of tube-shunt–associated endophthalmitis, we typically recommend tube-shunt explantation, as was performed in all 4 patients in this series, because of the risk of recurrent exposure and biofilm development.

The method of EMR database search for Kaplan-Meier analysis used in this study has several strengths and limitations. We used a Current Procedural Terminology- and ICD code-based search to identify eyes that underwent incisional glaucoma surgery and had associated endophthalmitis diagnoses, followed by focused chart review to confirm or exclude cases of filtering-associated endophthalmitis. This method allowed us to include a longer study period and greater number of eyes than would have been feasible if using a cohort or primary chart review method. Compared with a de-identified insurance-based search, our method allowed for chart confirmation of endophthalmitis diagnosis and determination of ophthalmology follow-up duration, 2 factors important in an accurate Kaplan-Meier analysis. Limitations include constraint of analysis to a single, large academic institution and the possibility of missing cases that were incorrectly coded.

In conclusion, we used an EMR database search to identify all eyes that underwent incisional glaucoma surgeries performed at a single academic institution over a recent 8-year period and found the rate of filtering-associated endophthalmitis to be persistent but relatively low. No significant difference was found in endophthalmitis rates when comparing trabeculectomy and tube-shunt implantation. Most patients with a poor visual acuity at presentation underwent PPV, and all patients with a tube shunt underwent explantation. No light perception vision and enucleation were avoided in all patients. Overall, high suspicion and prompt treatment result in the best prognosis in these uncommon patients.

Footnotes and Disclosures

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Analysis and interpretation: Simonett, Choi, Flaxel
Data collection: Simonett
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Overall responsibility: Simonett, Choi, Flaxel

Abbreviations and Acronyms:
EMR = electronic medical record; **HM** = hand movements; **ICD** = International Classification of Diseases; **NLP** = no light perception; **PPV** = pars plana vitrectomy.

Keywords:
Endophthalmitis, Filtering-associated infection, Trabeculectomy, Tube-shunt implantation.

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