Long-Term Bleb-Related Infections After Trabeculectomy: Incidence, Risk Factors, and Influence of Bleb Revision

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• PURPOSE: To report the incidence of late-onset bleb-related infections and to identify risk factors for bleb-related infections after trabeculectomy for the treatment of glaucoma.

• DESIGN: Retrospective case series.

• METHODS: Bleb-related infections were defined as blebitis, endophthalmitis, or blebitis with endophthalmitis. A total of 1959 eyes of 1423 patients who underwent trabeculectomy and who were followed for ≥1 year were included.

• RESULTS: Twenty-four eyes were diagnosed with bleb-related infections; 15 eyes were found to have blebitis and 9 eyes presented with endophthalmitis during the follow-up period of 5.4 ± 3.5 years (mean ± standard deviation). Among 15 eyes with blebitis, 2 eyes developed endophthalmitis under treatment. The Kaplan-Meier estimated incidence of bleb-related infections was 2.0% ± 0.5% (mean ± standard error) at 10 years. A Cox multivariate analysis showed the significant risk factors for a bleb-related infection to be diagnoses of pigmentary glaucoma or juvenile glaucoma, history of bleb leak, intraocular pressure sustained below the target pressure, chronic blepharitis, and the presence of punctal plugs. Surgical bleb revision demonstrated a protective effect against bleb-related infections ($P < .01$) when risk factors were present.

• CONCLUSIONS: This large case series with long-term follow-up demonstrates the incidence of bleb-related infections to be less than 2%, and describes the risk factors associated with bleb-related infections. A protective effect of surgical bleb revision was demonstrated. Clinicians should be constantly vigilant for, and patients made aware of, the possibility of bleb-related infections long after trabeculectomy, especially in the presence of identified risk factors. (Am J Ophthalmol 2015;159(6): 1082–1091. © 2015 by Elsevier Inc. All rights reserved.)

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LATE-ONSET BLEB-RELATED INFECTION IS A POTENTIALLY devastating complication after trabeculectomy. While the overall incidence varies among different studies according to the study design, follow-up period, surgical technique, and statistical methods, the incidence of late postoperative infections is higher than with most other intraocular surgeries.[1] With the widespread use of antiproliferative agents like mitomycin C (MMC) or 5-fluorouracil (5-FU) to enhance surgical success rates, a higher incidence of bleb-related infections has been noted compared to before their introduction, which had been reported to be 0.2%–1.5%.[2–4] The incidence reported for MMC-augmented trabeculectomy with follow-up periods of 1–12 years varies between 1.1% and 13.8% and that for intraoperative 5-FU-augmented trabeculectomy with follow-up of 16 months - 18 years ranges from 0.8% to 13.0%.[5–11] The Kaplan-Meier estimated incidence at 5 years varies from 1.5% to 6.3% for blebitis and from 1.1% to 7.5% for bleb-related endophthalmitis in several studies.[11–13] Although it is evident that bleb-related infections can develop long after trabeculectomy (up to 42 years after),[14] and the cumulative incidence seems to increase linearly with time, the estimated risks of this complication have not been reported beyond 5 years.[11–13]

Many investigators have evaluated presumed risk factors for the occurrence of bleb-related infections through case-control studies, case series without survival analysis, or case series with survival analysis. In a number of case-control studies, use of postoperative antibiotics, late-onset bleb leak, younger age, black race, and inferior location of the filtering bleb were shown to be associated with a significant risk of bleb-related infections.[15–18] The largest retrospective case series so far has been reported by Sharan and associates. An analysis of 521 cases in a mean follow-up of 5.3 years revealed that bleb leak, black race, and bleb manipulation were important risk factors for bleb-related infections.[10] A notable study that used survival analysis was the Collaborative Bleb-Related Infection Incidence and Treatment Study by Yamamoto and associates.[12] It was a prospective, multicenter study including 1098 eyes of 1098 patients who underwent a superior trabeculectomy with MMC, and it demonstrated a 5-year incidence of 2.2%, with significant risk factors being bleb leak and younger age.[12]

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Since many complications after trabeculectomy are known to be associated with bleb-related infections,[15,19–24] surgical bleb revision might affect the cumulative incidence of late complications. No published studies have reported the influence of surgical bleb revision on the incidence of bleb-related infections.

We report the long-term estimated incidence of late-onset bleb-related infections at 10 years with survival analysis of a large case series. We estimate the hazard ratios for presumed risk factors of bleb-related infections and investigate the influence of surgical bleb revision on bleb-related infection risk, based on a survival analysis of long-term results in patients who underwent trabeculectomy with adjuvant MMC or 5-FU at a single tertiary glaucoma care center.

METHODS

• **ELIGIBILITY CRITERIA AND DETERMINATION OF FOLLOW-UP PERIOD:** This retrospective case series was conducted in accordance with the tenets set forth in the Declaration of Helsinki and was approved by the Institutional Review Board at UCLA before the study began. Eyes that underwent trabeculectomy with intraoperative use of either MMC or 5-FU during the time interval between December 1993 and March 2013 and that were followed up for ≥1 year at the Jules Stein Eye Institute were included in the study. Eyes that underwent subsequent implantation of a glaucoma drainage device within the first postoperative year and those with a history of previous endophthalmitis or blebitis were excluded.

The follow-up period was determined as the interval between trabeculectomy and the last office visit. Intraocular surgeries such as the insertion of a glaucoma drainage device, scleral buckling, vitrectomy, combined surgery, or development of malignant glaucoma or phthisis marked the end of follow-up (ie, that eye was censored). The occurrence of a bleb-related infection was the event of interest (ie, failure), and the follow-up period was determined to be less than 1 year for those eyes that developed bleb-related infections during the first postoperative year. If both eyes of the same patient were eligible, both eyes were included in the study.

• **SURGICAL TECHNIQUE:** All eyes were operated with peribulbar anesthesia with 2–4 mL of 2% lidocaine. A conjunctival flap was created superiorly in either a fornix-based or limbus-based manner. The location of the bleb was determined from the operative notes. Typically, a superior peritomy was created about 4 clock hours (from 10 o'clock to 2 o'clock) wide for fornix-based flaps. For limbus-based flaps, the conjunctiva just anterior to the superior rectus insertion was elevated and cut, then the incision was extended temporally and nasally for a total of 8–10 mm. The Tenon capsule was then elevated and incised in a similar fashion. Exceptions occurred in 5 eyes where the blebs were made in the superonasal quadrant and in 1 eye where the bleb was made in the superotemporal quadrant. A scleral rectangular flap (approximately 3 × 3 mm) was outlined with light wet-field cautery. The episcleral bed was dried and a large (approximately 6 × 12 mm) Merocel sponge(Beaver-Visitec International Inc, Waltham, MA) soaked in either MMC (0.2–0.4 mg/mL) or 5-FU (50 mg/mL) was applied to the episcleral bed for 0.25–5 minutes.

After removal of the sponge, the exposed episcleral and Tenon areas were copiously irrigated with balanced salt solution. A partial-thickness scleral flap hinged at the superior limbus was made. A trabecular meshwork/corneal block 1 × 2 mm in size was resected under the anteriormost portion of the scleral flap. A basal iridectomy was performed and the scleral flap was sutured with 2–5 interrupted sutures to approximate the scleral flap onto the scleral bed. The conjunctiva was placed back and sutured in a watertight fashion. A paracentesis was made and the bleb was elevated by injecting balanced salt solution into the anterior chamber. The eye was inflated to a physiologic pressure with the anterior chamber completely formed. All surgery was performed by 5 glaucoma specialists at Jules Stein Eye Institute. Topical antibiotic eye drops were prescribed for 1 week after surgery and topical corticosteroids were used for 4–6 weeks postoperatively. Laser suture lysis was performed as needed with a diode laser from 1 to 6 weeks postoperatively. All patients were advised to avoid the use of contact lenses postoperatively.

Bleb revision was performed for the treatment of high thin blebs, bleb dysesthesia, bleb leak, and overfiltering blebs with hypotony maculopathy. The technique of surgical bleb revision followed a method previously reported.[24] Resuturing of the trabeculectomy flap was performed in most of the revisions; in some cases a pericardial graft was required to reinforce the sclera. When indicated, drainage of choroidal effusions and reformation of the anterior chamber was also performed.

• **DATA COLLECTION AND DEFINITION OF PARAMETERS:** Data were collected by retrospective review of medical records. Table 1 describes the clinical and demographic characteristics of the patients. Those with a history of any organ transplantation, chronic administration of oral corticosteroid or immunosuppressant, who were on chemotherapy, who were diagnosed as having seropositive human immunodeficiency virus (HIV), end-stage renal disease, or diabetes mellitus were considered to be immunocompromised.

The cut-off time used to differentiate between early leak and late leak was 6 postoperative weeks. Hypotony was defined as intraocular pressure (IOP) less than 5 mm Hg, measured by Goldmann applanation tonometry, on 2 consecutive visits at 6 weeks or later postoperatively. Prolonged hypotony was defined as IOP less than 5 mm Hg, measured by Goldmann tonometry, on more than 3 consecutive visits and longer than 3 months. Chronic

TABLE 1. Results From Survival Analysis of Eyes That Underwent Trabeculectomy

Parameter	Total Number of Eyes	Number of Bleb-Related Infections (%)	Log-Rank Test	Generalized Estimating Equation
Demographic characteristics				
Sex[a]				
Male	857	7 (0.8)	.159	.151
Female	1102	17 (1.5)		
Age[a]				
≥50 years	1761	18 (1.0)	.044	.074
<50 years	198	6 (3.0)		
Race			.298	.210
White	1160	17 (1.5)		
Asian	276	5 (1.8)		
Black	185	1 (0.5)		
Hispanic & others	338	1 (0.3)		
Systemic conditions				
Diabetes mellitus				
No	1766	21 (1.2)	.524	.546
Yes	193	3 (1.6)		
Hypertension				
No	1396	18 (1.3)	.895	.895
Yes	563	6 (1.1)		
Immunocompromised state (diabetes included)				
No	1756	21 (1.2)	.634	.646
Yes	203	3 (1.5)		
Types of glaucoma[a]			.000	.000
POAG	1411	15 (1.1)		
PACG	141	1 (0.7)		
Pigmentary glaucoma	39	4 (10.3)		
Juvenile glaucoma	18	2 (11.1)		
All other secondary	350	2 (0.6)		
Lens status				
Phakic	1309	19 (1.5)	.311	.293
Pseudophakic, aphakic	650	5 (0.8)		
Laterality				
OD	977	11 (1.1)	.657	.656
OS	982	13 (1.3)		
Surgical factors				
Antimetabolites[a]				
MMC	1926	22 (1.1)	.019	.084
5-FU	33	2 (6.1)		
Application duration of MMC (min)				
MMC <3	1804	19 (1.0)	.365	.397
MMC ≥3	122	3 (0.2)		
Type of conjunctival flap				
Fornix	968	11 (1.1)	.597	.601
Limbus	991	13 (1.3)		
Two or more filtration surgeries				
No	1663	21 (1.3)	.422	.398
Yes	296	3 (1.0)		
Previous trabeculectomy				
No	1857	24 (1.3)	NA	NA
Yes	102	0 (0.0)		

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TABLE 1. Results From Survival Analysis of Eyes That Underwent Trabeculectomy (*Continued*)

Parameter	Total Number of Eyes	Number of Bleb-Related Infections (%)	Log-Rank Test	Generalized Estimating Equation
Postoperative interventions				
Laser suture lysis				
No	1183	18 (1.5)	.371	.359
Yes	776	6 (0.8)		
Needling and/or 5-FU injection				
No	1843	23 (1.2)	.717	.703
Yes	116	1 (0.9)		
Bleb revision				
No	1791	22 (1.2)	.759	.752
Yes	168	2 (1.2)		
Surgical complications				
Early leak[a]				
No	1797	18 (1.0)	.003	.013
Yes	162	6 (3.7)		
Shallow or flat anterior chamber				
No	1861	24 (1.3)	NA	NA
Yes	98	0 (0.0)		
Hypotony maculopathy				
No	1899	23 (1.2)	.905	.906
Yes	60	1 (1.7)		
Choroidal effusion[a]				
No	1693	17 (1.0)	.056	.082
Yes	266	7 (2.6)		
Hyphema[a]				
No	1751	17 (1.0)	.018	.037
Yes	208	7 (3.4)		
Hypotony[a]				
No	1581	15 (0.9)	.127	.145
Yes	378	9 (2.4)		
Prolonged hypotony				
No	1880	22 (1.2)	.516	.384
Yes	79	2 (2.5)		
Late leak (positive Seidel)[a]				
No	1854	8 (0.4)	.000	.000
Yes	105	16 (15.2)		
Cataract surgery during follow-up				
No	1215	12 (1.0)	.707	.707
Yes	744	12 (1.6)		
Bleb morphology				
Avascular bleb				
No	1177	2 (0.2)	.000	.000
Yes	782	22 (2.8)		
High bleb				
No	1909	20 (1.0)	.001	.012
Yes	50	4 (8.0)		
Thin-walled bleb				
No	1441	5 (0.3)	.000	.000
Yes	518	19 (3.7)		
Low bleb				
No	1282	22 (1.7)	.006	.002
Yes	678	2 (0.3)		

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TABLE 1. Results From Survival Analysis of Eyes That Underwent Trabeculectomy (*Continued*)

Parameter	Total Number of Eyes	Number of Bleb-Related Infections (%)	Log-Rank Test	Generalized Estimating Equation
Fully functioning bleb[a]				
No	841	2 (0.2)	.000	.000
Yes	1118	22 (2.0)		
Blepharitis				
Total blepharitis				
No	1741	18 (1.0)	.082	.115
Yes	218	6 (2.8)		
Chronic blepharitis[a]				
No	1917	21 (1.1)	.001	.016
Yes	42	3 (7.1)		
Episodic blepharitis				
No	1783	21 (1.2)	.798	.801
Yes	176	3 (1.7)		
Chronic use of oral steroid				
No	1929	24 (1.2)	NA	NA
Yes	30	0 (0.0)		
Use of punctal plugs[a]				
No	1921	22 (1.1)	.011	.068
Yes	38	2 (5.3)		
Groups[a]			.000	.000
Group 1[b]	1661	10 (0.6)		
Group 2[c]	167	1 (0.6)		
Group 3[d]	131	13 (9.9)		

5-FU = 5-fluorouracil; MMC = mitomycin C; NA = not applicable (all cases are censored); PACG = primary angle closure glaucoma; POAG = primary open-angle glaucoma.

P values from the univariate log-rank test and the generalized estimating equation are shown for each parameter.

[a]Factors entered into multivariate analysis.

[b]Group 1: eyes without risk factors.

[c]Group 2: eyes with risk factors and that had surgical bleb revision.

[d]Group 3: eyes with risk factors but with no revision having been performed.

blepharitis was defined as the existence of more than 3 episodes of lid inflammation that lasted for more than 6 cumulative months.

Bleb morphology followed the descriptions provided by the examining physicians at the end of follow-up; these included "avascular bleb," "high and/or large bleb," "thin-walled bleb," and "low bleb." When the morphology of blebs was not described in medical records, we assumed that there was nothing remarkable about the bleb. However, factors regarding morphologic descriptions were excluded from multivariate regression, for they were not available in as many as 24% of the cases. We defined a "fully functioning bleb" as one that was sufficient to maintain the IOP below the predetermined target level without IOP-lowering medications, including no oral carbonic anhydrase inhibitors (CAIs).

To measure the influence of bleb revision on the incidence of bleb-related infections, eyes were grouped into 3 categories: eyes without risk factors (Group 1), eyes with risk factors and that had surgical bleb revision (Group 2), and eyes with risk factors but with no revision having been performed (Group 3). Risk factors included a history of late bleb leak prior to the diagnosis of bleb-related infections, prolonged hypotony accompanied by hypotony maculopathy or chronic choroidal detachment, and large or high blebs.

• **EVENT (BLEB-RELATED INFECTIONS) DETECTION, MICROBIOLOGIC RESULTS, AND TREATMENT:** Blebitis was defined as presenting symptoms of ocular discomfort and increased redness, with a clinical appearance of white, mucopurulent, or opaque blebs with loss of translucency, conjunctival injection surrounding the bleb, and cells in the anterior chamber. In addition, presence of hypopyon or robust anterior chamber cellular reaction, or inflammatory cells in the anterior vitreous, were considered to be endophthalmitis. Clinical presentation of either blebitis or endophthalmitis was defined as an event (bleb-related

infections). Samples for microbiologic culture were obtained from the anterior chamber when the eyes presented with blebitis and from the anterior chamber and vitreous when they presented with endophthalmitis. Samples were inoculated in aerobic media, anaerobic media, and fungal media (blood, R2A, Sabouraud's dextrose agar as solid-phase media with cooked meat, brain-heart infusion, thioglycolate broth used as enrichment media). Testing for antibiotic susceptibility was done simultaneously. Conjunctival cultures were not generally performed.

Bleb-related infections were diagnosed clinically and prompt empirical antibiotic treatment was initiated until culture results became available. Alternate use of fortified vancomycin 25 mg/mL and tobramycin 15 mg/mL (or cefazoline 50 mg/mL and tobramycin 15 mg/mL) eye drops every 30–60 minutes was initiated, followed by substitution with fluoroquinolone (0.5% gatifloxacin, 0.5% moxifloxacin, or 0.3% ofloxacin) eye drops. Surgical bleb revision was performed to correct coexisting bleb leaks after the infection resolved.

A regimen of either vancomycin (1 mg/0.1 mL) with amikacin (0.4 mg/0.1 mL) and dexamethasone (0.4 mg/0.1 mL) or vancomycin 1 mg/0.1 mL with ceftazidime (2.25 mg/0.1 mL) and dexamethasone (0.4 mg/0.1 mL) was used for intravitreal injections. Pars plana vitrectomy was performed for intractable or virile infections combined with other treatments.

• **STATISTICAL METHODS:** The estimated incidence of bleb-related infections was calculated with Kaplan-Meier survival analysis, which accounts for the loss of follow-up among study eyes. Relative risks were determined with a univariate Mantel-Cox log-rank test. A multivariate Cox regression model and time-dependent Cox model were used to calculate the hazard ratios of presumed risk factors. Generalized estimating equation linear models, which are generally used to extract the appropriate amount of information from correlated data, were used, to take into account the correlation between fellow eyes of the same patient.[25] For comparison of means, we used an independent samples *t* test. All statistical analyses were conducted with IBM SPSS, version 22.0 (IBM Corp., Armonk, NY) and the open programming language R version 3.1.1.

RESULTS

A TOTAL OF 1959 EYES OF 1423 PATIENTS WERE INCLUDED IN this study. Patients underwent 2084 superiorly located trabeculectomies with intraoperative MMC or 5-FU during the interval between December 1993 and March 2013 and were followed up for ≥1 year. Among the otherwise eligible eyes during the study period, 151 eyes were excluded because they were followed for less than a year. Forty-one eyes were also excluded because they underwent intraocular surgeries

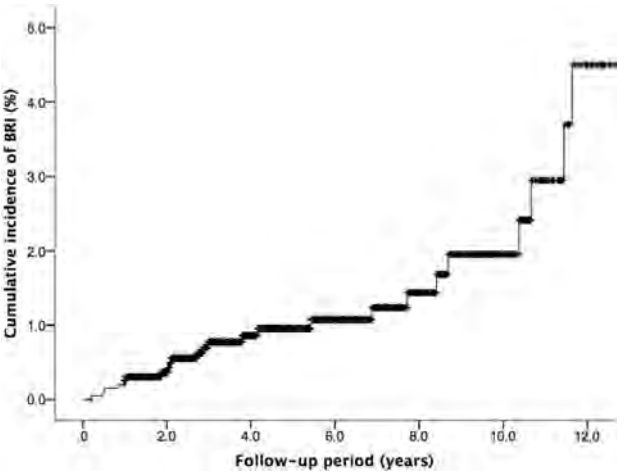

FIGURE 1. The Kaplan-Meier cumulative incidence of bleb-related infections (event) in 1959 eyes that underwent trabeculectomy for the treatment of glaucoma. Events occurred in 24 eyes and the last event was at 11.6 years after trabeculectomy.

such as the insertion of a glaucoma drainage device, scleral buckling, combined surgery, or vitrectomy during the first postoperative year.

The mean (±SD) follow-up period was 5.4 ± 3.5 years (range: 0.2–17.9 years). The follow-up period contains 4 eyes that developed bleb-related infections during the first postoperative year. There was no previous history of incisional intraocular surgery in 1257 eyes. Six hundred and fifty eyes had prior cataract surgery, 51 eyes had prior refractive surgery, 35 eyes had prior vitrectomy, and 22 eyes had prior penetrating keratoplasy or Descemet stripping endothelial keratoplasty. Forty-nine eyes had a history of 2 or more surgeries.

Twenty-four of 1959 eyes (1.2%) were diagnosed with bleb-related infections; 15 eyes presented with blebitis and 9 eyes presented with blebitis and endophthalmitis. Among the 15 eyes with blebitis, 2 eyes developed endophthalmitis despite treatment. The interval between the surgery and onset of bleb-related infections was 4.6 ± 3.9 years (range: 0.2–10.7 years). Demographic characteristics, clinical manifestations, complications, and methods of treatment for 24 eyes with bleb-related infections are summarized in Table 1. The Kaplan-Meier estimated incidence of bleb-related infections was 2.0% ± 0.5% (mean ± standard error) at 10 years and the cumulative incidence of bleb-related infections over time increased linearly throughout the follow-up period of 12 years (Figure 1). Surgical bleb revision was performed once in 153 eyes, twice in 13 eyes, and 3 times in 2 eyes. The most common cause for surgical bleb revision was late bleb leak (67/168 eyes, 39.9%); other causes were prolonged hypotony (41/168 eyes, 24.4%), hypotony maculopathy (39/168 eyes, 23.2%) and bleb dysesthesia or dellen caused by high or large blebs (21/168 eyes, 12.5%). Concomitant procedures performed with surgical bleb revision were

TABLE 2. Results From Cox Multivariate Regression of Eyes That Underwent Trabeculectomy (Event Defined as the Development of a Bleb-Related Infection)

Parameters	Hazard Ratio	95% Confidence Interval	*P*
Diagnosis (reference: POAG)			
ACG	0.19	0.023–1.6	.133
Pigmentary glaucoma	10.3	3.008–35	.000
Juvenile glaucoma	6.5	1.2–34	.027
All other secondary	0.29	0.058–1.5	.138
Early leak (reference: no leak)	4.0	1.4–11	.009
Late leak (reference: no leak)	170	37–790	.000
Fully functioning bleb (reference: not fully functioning bleb)	11	2.0–59	.006
Chronic blepharitis (reference: no blepharitis)	7.6	2.0–29	.003
Use of punctal plugs (reference: no use)	6.1	1.3–29	.022
Group (reference: Group 3[a])			
Group 1[b]	4.1	0.8–20	.079
Group 2[c]	0.019	0.002–0.19	.001

ACG = angle closure glaucoma; POAG = primary open-angle glaucoma.

Parameters with *P* values .20 or less in the univariate log-rank test were entered into the model. Only the statistically significant parameters are shown.

[a]Group 3: eyes with risk factors but no revision having been performed.

[b]Group 1: eyes without risk factors.

[c]Group 2: eyes with risk factors and that had surgical bleb revision.

drainage of choroidal effusion in 5 cases, anterior chamber reformation in 4 cases, and removal of a fibrous membrane from the anterior chamber in 2 cases. The mean age (±SD) of 57 eyes with juvenile glaucoma and pigmentary glaucoma was significantly younger (46.4 ± 17.5 years) than those with other types of glaucoma (68.1 ± 13.0 years) ($P < .001$).

P values from the univariate log-rank test and those from the generalized estimating equation are shown side by side for each parameter in Table 1. Age less than 50 years was a predisposing factor for bleb-related infections ($P < .05$). The risk of bleb-related infections was significantly different among different types of glaucoma ($P < .001$). Eyes with early or late leaks, hyphema, intraoperative 5-FU use, and use of punctal plugs were at higher risk. Avascular, high, or thin-walled blebs also had a higher risk for infection ($P < .01$). Eyes with chronic blepharitis were at higher risk ($P < .01$), but episodic blepharitis seemed not to be associated with bleb-related infections ($P < .05$). Fully functioning blebs showed a higher risk ($P < .001$), and there was a statistically significant difference among Group 1, Group 2, and Group 3 ($P < .001$) (Table 1).

Parameters with *P* values of .20 or less in the log-rank test were entered into a Cox multivariate regression. The forward: conditional method was used in the model and only the significant parameters are shown in Table 2. The hazard ratios of pigmentary glaucoma and juvenile glaucoma as compared to primary open-angle glaucoma were 10.3 (95% confidence interval: 3.008–35, $P < .001$) and 6.5 (95% confidence interval: 1.2–34, $P < .05$), respectively. Late bleb leak was associated with a higher hazard ratio than early bleb leak (hazard ratio = 170, 95% confidence interval: 37–790, $P < .001$ vs hazard ratio = 4.0, 95% confidence interval: 1.4–11, $P < .01$). Fully functioning blebs, chronic blepharitis, and the use of punctual plugs were also associated with a higher risk of bleb-related infections on multivariate analysis (Table 2).

The hazard ratio of Group 2 (ie, eyes with risk factors and who had surgical bleb revision) to Group 3 (ie, eyes with risk factors but no revision having been performed) was 0.019 (95% confidence interval: 0.002–0.19, $P < .01$) (Figure 2).

DISCUSSION

OUR STUDY REPRESENTS ONE OF THE LARGEST CASE SERIES in the literature with long-term follow-up and reports the Kaplan-Meier estimates for the incidence of bleb-related infections beyond 5 years after trabeculectomy. The estimated incidence at 10 years in this study (2.0%) is markedly lower than that of earlier reports from the 5-FU and MMC era.[5,7,8,11,26,27] Shorter duration of antimetabolite application with a large Merocel sponge may have contributed to the lower incidence of bleb-related infections, as in the report by Yamamoto and associates.[12] Since the outcome of filtration surgery can be affected by the extent of the subconjuctival area of antimetabolite

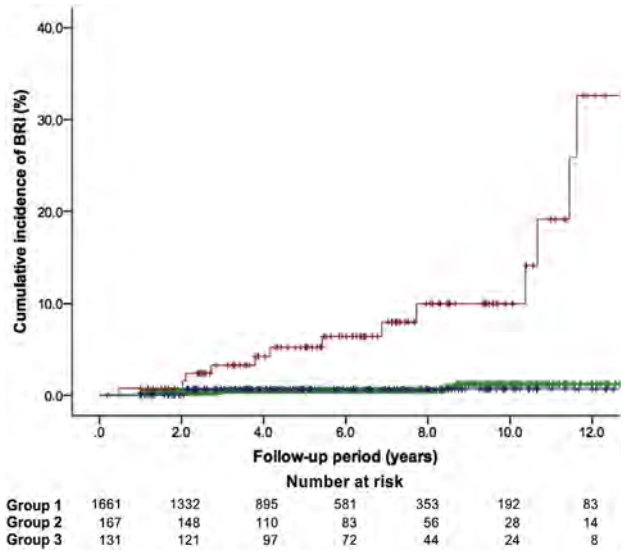

FIGURE 2. The Kaplan-Meier cumulative risks of bleb-related infections after trabeculectomy for the treatment of glaucoma, for each group of eyes: Group 1, eyes without risk factors (green line); Group 2, eyes with risk factors and that had surgical bleb revision (blue line); and Group 3, eyes with risk factors but no revision having been performed (red line).

application,[28] it is important for clinicians to consider lower doses of antimetabolites, shorter durations of application, and large areas of exposure.

Risk factors for bleb-related infections have been reported. Some of these include: inferiorly placed blebs,[8] avascular blebs,[7] thin-walled blebs,[29–31] the use of antiproliferative agents,[16,18] a history of bleb leak,[15,18] postoperative flat anterior chamber,[18] suprachoroidal hemorrhage,[18] blepharitis,[32] younger age,[33] black race,[10] hypotony,[27] nasolacrimal duct obstruction,[27] juvenile glaucoma,[18] and chronic use of topical antibiotics.[18] This study evaluated risk factors with a multivariate Cox regression analysis to adjust for possible confounding effects of all variables. Diagnoses of juvenile glaucoma and pigmentary glaucoma were revealed to be significant risk factors. Nasolacrimal duct obstruction is known to be associated with bleb-related infections,[27] but our study showed that use of punctal plugs to treat dysfunctional tear syndrome could also increase the incidence of bleb-related infections (Table 2). Blepharitis is known to be related to bleb-related infections[32]; blepharitis of fewer than 3 episodes lasting less than a cumulative period of 6 months (episodic blepharitis) did not demonstrate a significant predisposition in our data (Table 1).

Fully functioning blebs were more prone to bleb-related infections in our study. Yamamoto and associates introduced the term "well-functioning bleb" as one with sustained IOP less than 15 mm Hg without glaucoma medications, except oral CAIs for the fellow eye.[34] We defined a bleb achieving IOP less than target IOP with no medications including no oral CAIs as a "fully functioning bleb." This result is consistent with a few previous reports that have shown that eyes with low IOP on no medications are at the greatest risk for bleb-related infections.[10,12,18,35]

Late bleb leak has been consistently suggested as one of the most important risk factors for bleb-related infections.[15,36] Our multivariate analysis showed that bleb leak at any time after trabeculectomy can be hazardous. However, the hazard ratio of late bleb leak (after 6 postoperative weeks) was much higher (170, 95% confidence interval: 37–790, $P < .001$), than that of early bleb leak (4.0, 95% confidence interval: 1.4–11, $P < .01$). It is unknown whether the breakdown of the bleb allows entry of pathogenic organisms into the eye, or whether bacterial pathogens create a dehiscence in the conjunctiva after infection.[18] In our study, 5 eyes had a previous history of late bleb leak, and a leak within 1 week before the onset of infection was observed in 3 of them. Simultaneous bleb leak at the time of diagnosis was seen in 11 eyes. In 3 eyes, previously undetected bleb leak was demonstrated after the diagnosis of a bleb-related infection.

Efforts have been made to effectively prevent this potentially vision-threatening complication. Education of patients for early detection and prompt treatment of bleb-related infections has been implemented.[32,37] Long-term use of topical antibiotics seems to be detrimental and has been reported to increase the rate of bleb-related infections.[18] Surgical bleb revision should be considered for patients with bleb leak, overfiltration, and blebs with excessive height or extent.[15,19–24] The incidence of bleb-related infections after bleb revision ranged from 0% to 5% within follow-up periods from 2.3 to 4.7 years.[19–21] Burnstein and associates observed bleb-related infections in 6 of 37 eyes that received conservative treatment for such complications, but no bleb-related infection occurred in eyes that had undergone surgical bleb revision.[38] Our study showed that the hazard ratio of Group 2 (ie, eyes with risk factors and that had surgical bleb revision) was 0.019 (95% confidence interval: 0.002–0.19, $P < .01$), compared to Group 3 (ie, the eyes with risk factors but no revision having been performed). Our findings demonstrate that surgical bleb revision exerts a protective effect against bleb-related infections when 1 or more risk factors are present.

A limitation of our study is that the results represent patients of 1 glaucoma subspecialty practice in a specific geographic location. In addition, because of the retrospective nature of the data collection from medical records, there was no standard grading of bleb morphology. The lack of a morphologic description of blebs in 24% of cases also prevented us from adding specific bleb morphologies into the Cox multivariate regression. The number of eyes excluded from this study owing to insufficient follow-up was not excessive (151 eyes), so that the potential influence of ascertainment bias was minimized. Also, the incidence of bleb-related infections was estimated with a Kaplan-Meier analysis, which assumes that eyes lost to follow-up are random (ie, the incidence risk is the same for lost and

followed eyes). Although we cannot validate this assumption based on our data, it is a commonly accepted assumption for all such analyses.

In summary, we demonstrated a comparatively low estimated incidence of bleb-related infections at 10 years after trabeculectomy. Risk factors for bleb-related infections were consistent with previous reports. Diagnoses of pigmentary glaucoma or juvenile glaucoma and the use of punctal plugs were associated with significantly high hazard ratios. This study also shows that surgical bleb revision exerts a protective effect against bleb-related infections (Table 2). The risk for bleb-related infections continues for the lifetime of a functioning bleb.[39] Therefore, clinicians should be continuously vigilant for, and patients made aware of, the possibility of bleb-related infections long after trabeculectomy, especially in the presence of identified risk factors.

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REFERENCES

1. Prasad N, Latina MA. Blebitis and endophthalmitis after glaucoma filtering surgery. *Int Ophthalmol Clin* 2007;47(2):85–97.
2. Katz LJ, Cantor LB, Spaeth GL. Complications of surgery in glaucoma. Early and late bacterial endophthalmitis following glaucoma filtering surgery. *Ophthalmology* 1985;92(7):959–963.
3. Freedman J, Gupta M, Bunke A. Endophthalmitis after trabeculectomy. *Arch Ophthalmol* 1978;96(6):1017–1018.
4. Solomon A, Ticho U, Frucht-Pery J. Late-onset, bleb-associated endophthalmitis following glaucoma filtering surgery with or without antifibrotic agents. *J Ocul Pharmacol Ther* 1999;15(4):283–293.
5. Ticho U, Ophir A. Late complications after glaucoma filtering surgery with adjunctive 5-fluorouracil. *Am J Ophthalmol* 1993;115(4):506–510.
6. Uchida S, Suzuki Y, Araie M, Shigeeda T, Hara T, Shirato S. Long-term follow-up of initial 5-fluorouracil trabeculectomy in primary open-angle glaucoma in Japanese patients. *J Glaucoma* 2001;10(6):458–465.
7. Mochizuki K, Jikihara S, Ando Y, Hori N, Yamamoto T, Kitazawa Y. Incidence of delayed onset infection after trabeculectomy with adjunctive mitomycin C or 5-fluorouracil treatment. *Br J Ophthalmol* 1997;81(10):877–883.
8. Greenfield DS, Suñer IJ, Miller MP, Kangas TA, Palmberg PF, Flynn HW. Endophthalmitis after filtering surgery with mitomycin. *Arch Ophthalmol* 1996;114(8):943–949.
9. Shigeeda T, Tomidokoro A, Chen Y-N, Shirato S, Araie M. Long-term follow-up of initial trabeculectomy with mitomycin C for primary open-angle glaucoma in Japanese patients. *J Glaucoma* 2006;15(3):195–199.
10. Sharan S, Trope GE, Chipman M, Buys YM. Late-onset bleb infections: prevalence and risk factors. *Can J Ophthalmol* 2009;44(3):279–283.
11. DeBry PW, Perkins TW, Heatley G, Kaufman P, Brumback LC. Incidence of late-onset bleb-related complications following trabeculectomy with mitomycin. *Arch Ophthalmol* 2002;120(3):297–300.
12. Yamamoto T, Sawada A, Mayama C, et al. The 5-year incidence of bleb-related infection and its risk factors after filtering surgeries with adjunctive mitomycin C: collaborative bleb-related infection incidence and treatment study 2. *Ophthalmology* 2014;121(5):1001–1006.
13. Zahid S, Musch DC, Niziol LM, Lichter PR, Collaborative Initial Glaucoma Treatment Study Group. Risk of endophthalmitis and other long-term complications of trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS). *Am J Ophthalmol* 2013;155(4):674–680.e1.
14. Ciulla TA, Beck AD, Topping TM, Baker AS. Blebitis, early endophthalmitis, and late endophthalmitis after glaucoma-filtering surgery. *Ophthalmology* 1997;104(6):986–995.
15. Soltau JB, Rothman RF, Budenz DL, et al. Risk factors for glaucoma filtering bleb infections. *Arch Ophthalmol* 2000;118(3):338–342.
16. Lehmann OJ, Bunce C, Matheson MM, et al. Risk factors for development of post-trabeculectomy endophthalmitis. *Br J Ophthalmol* 2000;84(12):1349–1353.
17. Wallin Ö, Al-ahramy Abdullah M, Lundström M, Montan P. Endophthalmitis and severe blebitis following trabeculectomy. Epidemiology and risk factors; a single-centre retrospective study. *Acta Ophthalmol* 2014;92(5):426–431.
18. Jampel HD, Quigley HA, Kerrigan-Baumrind LA, et al. Risk factors for late-onset infection following glaucoma filtration surgery. *Arch Ophthalmol* 2001;119(7):1001–1008.
19. Radhakrishnan S, Quigley HA, Jampel HD, et al. Outcomes of surgical bleb revision for complications of trabeculectomy. *Ophthalmology* 2009;116(9):1713–1718.
20. Lin AP, Chung JE, Zhang KS, et al. Outcomes of surgical bleb revision for late-onset bleb leaks after trabeculectomy. *J Glaucoma* 2013;22(1):21–25.
21. Bitrian E, Song BJ, Caprioli J. Bleb revision for resolution of hypotony maculopathy following primary trabeculectomy. *Am J Ophthalmol* 2014;158(3):597–604.e1.
22. Baswati P, Samiksha C, Subodh S, Abhishek D. Revision of dysfunctional filtering bleb by conjunctival advancement with bleb preservation: a simple choice for massive choroidals with hypotony following trabeculectomy. *Saudi J Ophthalmol* 2013;27(4):287–290.

23. Budenz DL, Chen PP, Weaver YK. Conjunctival advancement for late-onset filtering bleb leaks: indications and outcomes. *Arch Ophthalmol* 1999;117(8):1014–1019.
24. Tannenbaum DP, Hoffman D, Greaney MJ, Caprioli J. Outcomes of bleb excision and conjunctival advancement for leaking or hypotonous eyes after glaucoma filtering surgery. *Br J Ophthalmol* 2004;88(1):99–103.
25. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 1988; 44(4):1049–1060.
26. Higginbotham EJ, Stevens RK, Musch DC, et al. Bleb-related endophthalmitis after trabeculectomy with mitomycin C. *Ophthalmology* 1996;103(4):650–656.
27. Song A, Scott IU, Flynn HW, Budenz DL. Delayed-onset bleb-associated endophthalmitis: clinical features and visual acuity outcomes. *Ophthalmology* 2002;109(5):985–991.
28. Cordeiro MF, Constable PH, Alexander RA, Bhattacharya SS, Khaw PT. Effect of varying the mitomycin-C treatment area in glaucoma filtration surgery in the rabbit. *Invest Ophthalmol Vis Sci* 1997;38(8):1639–1646.
29. Ashkenazi I, Melamed S, Avni I, Bartov E, Blumenthal M. Risk factors associated with late infection of filtering blebs and endophthalmitis. *Ophthalmic Surg* 1991;22(10):570–574.
30. Hattenhauer JM, Lipsich MP. Late endophthalmitis after filtering surgery. *Am J Ophthalmol* 1971;72(6):1097–1101.
31. Sugar HS, Zekman T. Late infection of filtering conjunctival scars. *Am J Ophthalmol* 1958;46(2):155–170.
32. Waheed S, Liebmann JM, Greenfield DS, et al. Recurrent bleb infections. *Br J Ophthalmol* 1998;82(8):926–929.
33. Wolner B, Liebmann JM, Sassani JW, Ritch R, Speaker M, Marmor M. Late bleb-related endophthalmitis after trabeculectomy with adjunctive 5-fluorouracil. *Ophthalmology* 1991;98(7):1053–1060.
34. Yamamoto T, Kuwayama Y, Collaborative Bleb-related Infection Incidence and Treatment Study Group. Interim clinical outcomes in the collaborative bleb-related infection incidence and treatment study. *Ophthalmology* 2011;118(3):453–458.
35. Mac I, Soltau JB. Glaucoma-filtering bleb infections. *Curr Opin Ophthalmol* 2003;14(2):91–94.
36. Susanna R, Takahashi W, Nicolela M. Late bleb leakage after trabeculectomy with 5-fluorouracil or mitomycin C. *Can J Ophthalmol* 1996;31(6):296–300.
37. Chen PP, Gedde SJ, Budenz DL, Parrish RK. Outpatient treatment of bleb infection. *Arch Ophthalmol* 1997;115(9): 1124–1128.
38. Burnstein AL, WuDunn D, Knotts SL, Catoira Y, Cantor LB. Conjunctival advancement versus nonincisional treatment for late-onset glaucoma filtering bleb leaks. *Ophthalmology* 2002;109(1):71–75.
39. Parrish R, Minckler D. "Late endophthalmitis"–filtering surgery time bomb? *Ophthalmology* 1996;103(8):1167–1168.

REPORTING VISUAL ACUITIES

The AJO encourages authors to report the visual acuity in the manuscript using the same nomenclature that was used in gathering the data provided they were recorded in one of the methods listed here. This table of equivalent visual acuities is provided to the readers as an aid to interpret visual acuity findings in familiar units.

Table of Equivalent Visual Acuity Measurements

Snellen Visual Acuities				
4 Meters	6 Meters	20 Feet	Decimal Fraction	LogMAR
4/40	6/60	20/200	0.10	+1.0
4/32	6/48	20/160	0.125	+0.9
4/25	6/38	20/125	0.16	+0.8
4/20	6/30	20/100	0.20	+0.7
4/16	6/24	20/80	0.25	+0.6
4/12.6	6/20	20/63	0.32	+0.5
4/10	6/15	20/50	0.40	+0.4
4/8	6/12	20/40	0.50	+0.3
4/6.3	6/10	20/32	0.63	+0.2
4/5	6/7.5	20/25	0.80	+0.1
4/4	6/6	20/20	1.00	0.0
4/3.2	6/5	20/16	1.25	−0.1
4/2.5	6/3.75	20/12.5	1.60	−0.2
4/2	6/3	20/10	2.00	−0.3

From Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94:91–96.