Incidence of delayed onset infection after trabeculectomy with adjunctive mitomycin C or 5-fluorouracil treatment

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Abstract

***Aims/background*—The introduction of the adjunctive use of antiproliferatives to trabeculectomy has greatly improved the success rate of this operation. Trabeculectomy with antiproliferative treatment, however, is usually associated with a cystic and thin walled filtering bleb, which may be more susceptible to infection. The objective of this study was to evaluate the incidence, clinical findings, and risk factors of delayed onset, bleb related infection after trabeculectomy with adjunctive mitomycin C (MMC) or 5-fluorouracil (5-FU) treatment.**

***Methods*—The records of 632 glaucoma patients who underwent 966 trabeculectomies, with and without the use of adjunctive MMC or 5-FU treatment, between January 1985 and February 1995 were analysed. The mean follow up period was 3.5 (2.4) years (range 0.1 to 11.2 years). The mean patient age was 54.8 (18.8) years (range 0 to 88 years).**

***Results*—Bleb related infection occurred in one of 76 trabeculectomies that did not receive antiproliferatives (1.3%), three of 228 treated with 5-FU (1.3%) trabeculectomies, and seven of 662 treated with MMC (1.1%). Five eyes developed blebitis; six eyes developed endophthalmitis. Bleb related infection developed an average of 3.1 (1.6) (range 0.4 to 6.0) years after trabeculectomy. All eyes had avascular or hypovascular blebs that were cystic in shape before infection and all eyes had reduced intraocular pressure. Early wound leaks and chronic, intermittent bleb leaks were identified to be risk factors for the bleb related infection.**

***Conclusion*—The incidence of delayed onset, bleb related infection after trabeculectomy with antiproliferative treatment is similar to that after trabeculectomy without antiproliferatives.**

(*Br J Ophthalmol* 1997;**81**:877–883)

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Accepted for publication
4 June 1997

Antiproliferative agents, 5-fluorouracil (5-FU) and mitomycin C (MMC), have markedly improved the success rate of glaucoma filtering surgery and are widely used to treat glaucomatous eyes with a poor surgical prognosis.[1–4]

Trabeculectomy with antiproliferatives is usually associated with a cystic and thin walled filtering bleb that may be more susceptible to infection than a thick walled bleb.[5 6] Antiproliferative treatment allegedly alters bleb reactivity to postoperative inflammation.[7] The bleb in a trabeculectomy supplemented by MMC treatment is more likely to be avascular than its 5-FU treated counterpart.[8] Hence, the susceptibility to infection may vary with the different antiproliferatives administered. We compared the results of trabeculectomy with 5-FU or MMC treatment with the results of trabeculectomy with no antiproliferative treatment to determine the incidence and risk factors of delayed onset bleb infection.

Materials and methods

In this retrospective study, we reviewed the records of 632 glaucoma patients (317 males, 315 females) who underwent trabeculectomy (966 procedures in 883 eyes, 429 right eyes and 454 left eyes) between 1 January 1985 and 28 February 1995 at the Department of Ophthalmology of Gifu University Hospital. Trabeculectomies without antiproliferatives were performed between January 1985 and November 1994. Trabeculectomies with 5-FU treatment were performed between May 1985 and April 1993. Trabeculectomies with MMC treatment were performed between April 1990 and February 1995. The procedures were performed by one of two glaucoma specialists (TY or YK). All patients were Japanese, except one white American who received a trabeculectomy with adjunctive use of MMC (0.1 mg). The types of glaucoma are summarised in Table 1 Clinical factors analysed included patient age, sex, type of glaucoma, site of filtration surgery, total dose of 5-FU or MMC, and the presence of early bleb leaks (within the first 6 postoperative weeks) or a leak at the onset of infection. Of the 632 patients in the study, 394 received follow up care at our department and 238 received follow up care from a referring ophthalmologist. Referring ophthalmologists provided data via questionnaire.

Patients were not included in the study if they had fewer than 30 days of follow up care or underwent trabeculectomy combined with cataract extraction with or without posterior chamber lens implantation.

Trabeculectomies without antiproliferatives were performed 76 times in 76 eyes of 66 patients—27 males and 39 females. Trabeculectomies with postoperative 5-FU treatment were performed 228 times in 211 eyes of 168 patients—85 males and 83 females. Trab-

Table 1 Subjects

Type of glaucoma	*No of patients*	*Sex (M/F)*	*No of trabeculectomies*	*Age (years) (mean (SD)) (range)*	*Follow up (years) (mean (SD)) (range)*
Normal tension	104	40/64	155	61.0 (11.5) (34 ~ 87)	3.2 (1.6) (0.2 ~ 10.3)
Primary open angle	199	123/76	356	56.5 (15.2) (17 ~ 85)	3.5 (2.1) (0.1 ~ 10.5)
Primary angle closure	73	13/60	94	65.9 (10.3) (28 ~ 88)	3.8 (2.8) (0.1 ~ 11.1)
Congenital	27	12/15	49	17.0 (17.9) (0 ~ 8.3)	5.0 (3.8) (0.2 ~ 11.2)
Developmental	42	23/19	67	27.3 (13.1) (9 ~ 68)	3.0 (2.2) (0.3 ~ 10.4)
Secondary					
Uveitis	44	20/24	61	55.2 (14.5) (16 ~ 80)	3.8 (2.9) (0.1 ~ 10.3)
ICE	5	2/3	8	52.0 (7.5) (42 ~ 62)	4.9 (3.5) (1.0 ~ 9.3)
Capsular	48	32/16	63	70.2 (7.8) (50 ~ 82)	3.2 (2.0) (0.1 ~ 8.7)
Neovascular	22	14/8	29	54.9 (13.9) (22 ~ 80)	2.9 (2.8) (0.1 ~ 10.7)
Others	68	38/30	84	49.7 (20.6) (0 ~ 84)	3.2 (2.4) (0.1 ~ 11.1)

ICE = iridocorneal endothelial syndrome.

Table 2 Demographic data

Antiproliferatives	*No of patients*	*Sex (M/F)*	*No of eyes*	*No of trabeculectomies*	*Age (years) (mean (SD)) (range; median)*	*Follow up (years) (mean (SD)) (range; median)*
None	66	27/39	76	76	57.2 (19.6) (0 ~ 84; 71)	4.4 (3.1) (0.1~11.2; 2.6)
5-Fluorouracil	168	85/83	211	228	50.3 (21.8) (0~84; 42)	4.4 (3.3) (0.1 ~ 10.5; 3.2)
Mitomycin C	448	233/215	634	662	55.7 (17.3) (0 ~ 88; 42)	2.9 (1.4) (0.1 ~ 6.0; 3.1)

eculectomies with intraoperative MMC application were performed 662 times in 634 eyes of 448 patients—233 males and 215 females. If a patient underwent more than one trabeculectomy, each procedure was counted.

The overall mean patient age was 54.8 (18.8) years (range 0 to 88 years); 328 patients were younger than 60 years of age**.** The overall mean follow up period was 3.5 (2.4) years (range 0.1 to 11.2 years). The mean (SD) patient age and follow up period by treatment group are shown in Table 2. In some patients, the follow up was less than 1 year because the patient died or underwent another trabeculectomy and/or cataract surgery.

Of the 966 trabeculectomies, 896 were performed in a superior quadrant and 70 were performed in an inferior quadrant. The most common postoperative complications were shallow anterior chamber (29.5%), choroidal detachment (18.5%), corneal epithelial defects (9.9%), and early wound leakage (9.8%) (Table 3). An additional postoperative complication was chronic or intermittent bleb leakage (8.5%). Of the 632 patients, 154 had systemic hypertension and 65 had diabetes mellitus, posing new sets of possible postoperative complications. Of the 966 trabeculectomies, 670 had no previous surgical intervention including corneal or intraocular surgery. Of the 966 trabeculectomies, 108 were performed in aphakic or pseudophakic eyes.

Trabeculectomy was performed according to a modified Cairns' technique.[9] The surgical technique and postoperative care were essentially the same in each group; the major modifications to the Cairns' procedure involved the anterior chamber reformation and the conjunctival wound closure, and were performed described elsewhere.[12]

Patients receiving 5-FU treatment were given 5 mg of 5-FU at the completion of surgery by subconjunctival injection using a 30 gauge needle, 90° to 180° away from the surgical site. The 5-FU was administered once a day throughout the first postoperative week, then once every other day for the second postoperative week. Thus, each patient received 50 mg of 5-FU in 2 weeks.

Patients receiving MMC treatment were given from 0.02 to 0.2 mg of the antiproliferative, as shown in Table 4. The MMC, dissolved in 0.5 ml of distilled water and absorbed by sponges (Spongel, Yamanouchi Pharmaceuticals, Tokyo, Japan), was applied for 5 minutes to the exposed tissues, including the posterior surfaces of the conjunctiva and Tenon's capsule, the scleral flap, and adjacent episcleral tissue after the preparation of the scleral flap. Care was taken to keep sponges not only under the conjunctival flap, but also beneath the scleral flap. After 5 minutes, all sponges were removed and the wound was irrigated with 250 ml of a balanced salt solution. A block of tissue containing the trabeculum was then excised.

After the trabeculectomies, 1.2 mg of dexamethasone sodium phosphate was injected subconjunctivally. A 1% solution of atropine was also given topically at the time of surgery. All patients received a topical medical regimen in the postoperative period including a 0.1% solution of topical betamethasone, a 1% solution of topical atropine sulphate, and antibiotic eyedrops. Drops of 0.3% micronomicin sulphate were given from 1985 to 1988, and drops of 0.3% ofloxacin were given after 1989.

Table 3 Rate (%) of complications

	No of trabeculectomies			
	None	*5-Fluorouracil*	*Mitomycin C*	*Total*
Corneal epithelial defect	2 (2.6)	76 (33.3)	9 (1.4)	87 (9.0)
Early wound leak	4 (5.3)	20 (8.8)	62 (9.4)	86 (8.9)
Shallow anterior chamber	21 (27.6)	84 (36.8)	115 (17.3)	220 (22.8)
Choroidal detachment	12 (15.8)	44 (19.3)	95 (14.4)	151 (15.6)

Systemic β lactam antibiotics were administered for 1 week, and systemic steroids were given in some cases. Eye patches and compression dressing were used in cases with a shallow anterior chamber.

The patients were hospitalised for 1 to 2 weeks. After their discharge, patients were seen every week during the first postoperative month, every 2 weeks during the second month, then at least once a month thereafter. The biomicroscopic examination performed as routine follow up care at our department included checking the depth of the anterior chamber, scanning for conjunctival leaks, measuring ocular tension with a Goldmann applanation tonometer, and inspecting the fundus. The betamethasone was tapered off within the first 3 month postoperative period. However, the topical use of antibiotics and/or steroids continued at the discretion of the glaucoma specialist. The long term antibiotic therapy was administered to patients with thin walled and leaky blebs at our institution, and we changed the antibiotics approximately once annually. We also advised the patients not to administer the antibiotics daily, but to use the antibiotics whenever conjunctival injection, pain, or decreased vision developed. Argon laser suture lysis or bleb needling procedures were performed in selected cases of increased intraocular pressure. Of the 966 trabeculectomies, 638 received long term antibiotic therapy. The most frequently used agents were 0.3% micronomicin sulphate drops and 0.3% ofloxacin drops.

Table 4 Rate (%) of infection and mitomycin C concentrations

Concentration	*No of cases*	*No of trabeculectomies*
0.02	0	53 (0)
0.04	0	1 (0)
0.05	0	15 (0)
0.1	4	375 (1.1)
0.2	3	218 (1.4)

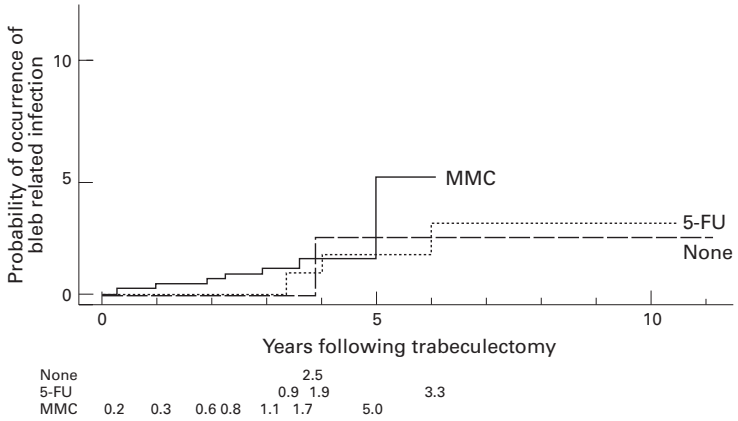

Figure 1 Kaplan–Meier estimation of bleb related infections.

The presence of characteristic white material within the bleb associated with surrounding conjunctival infection and intraocular inflammation indicated a bleb related infection. Patients were diagnosed as having blebitis in cases where bleb infection was presumed clinically without vitreous involvement.[10] We distinguished endophthalmitis from blebitis by the presence of vitreous involvement.

The incidence rate of bleb related infection and the incidence rate per patient year were calculated for the entire group. Separate incidence rates were determined for filtration surgery performed with and without adjunctive antiproliferative treatment; in addition, the rate of bleb related infection free survival was determined by using the Kaplan–Meier survival curve. Additional statistical analyses were performed using either Fisher's exact test or the χ^2 test to evaluate the differences in clinical factors between the groups, and relative risk was calculated by comparing the percentages of bleb related infection for each clinical factor. The statistical significance level was 0.05.

Results

Eleven eyes of 11 patients (six males, five females) developed bleb related infections. Of these 11 patients, four had primary open angle glaucoma, three had secondary glaucoma, two had developmental glaucoma, one had normal tension glaucoma, and one had capsular glaucoma (Tables 5a and b). Infection occurred in only one of 76 trabeculectomies that did not receive antiproliferatives (1.3%), in three of 228 trabeculectomies treated with 5-FU (1.3%), and in seven of 662 trabeculectomies treated with MMC (1.1%). Of these 11 cases of infection, five were diagnosed as blebitis and six were diagnosed as endophthalmitis.

Bleb infection developed an average of 3.1 (1.6) (range 0.4 to 6.0) years after the trabeculectomy. The mean follow up time before the onset of infection for patients treated with 5-FU was 4.5 (1.4) years and for patients treated with MMC it was 2.5 (1.5) years. There were no cases of early onset blebitis or endophthalmitis in the present study as defined by Katz *et al.*[11]

Of those patients with bleb related infection, the mean age of patients with 5-FU was 44.3 (15.2) years and the mean age of patients treated with MMC was 51.4 (21.7) years. Eight of the 11 patients were younger than 60 years old.

All patients presented with a white, milky bleb containing inflammatory material. In nine of the 11 cases, the right eye was the one infected. Patients presenting with a bleb related infection were hospitalised and treated appropriately for the extent of infection. Two patients (Nos 4 and 6) were treated at another university hospital or an eye clinic. Cultures of the conjunctival surface were obtained in all patients except one (No 6). Three eyes, which showed vitreal involvement on direct examination and on B-scan ultrasonography or ultrasound biomicroscopy, underwent vitrec-

Table 5a Summary of cases with bleb related infections

Patient No	Age (years)	Sex	Eye	Systemic diseases	Type of glaucoma	Number of previous operations	Site	Postoperative complications	Antiproliferative (dose (mg))	Seidel's test	Lens status	IOP controlled	Filtering bleb before onset	Onset of symptoms (y.mo)	Years to infection
1	58	F	R	hyperthyroidism, HTN	Secondary	0	Sup	shallow chamber, corneal epithelial defects	5-FU (50)	−	P	good	cystic, avascular	1989.6	3.4
2	47	M	L	DM	POAG	0	Sup	shallow chamber	5-FU (50)	+	P	good*	cystic, avascular	1991.11	4.0
3	38	F	R	none	Developmental	0	Sup	none	none	+	P	good	cystic, avascular	1993.4	3.9
4	15	F	L	none	Developmental	2	Sup	none	MMC (0.1)	−	P	good	cystic, avascular	1993.4	1.1
5	75	M	R	HTN	NTG	0	Sup	wound leakage, choroidal detachment	MMC (0.1)	−	A	good	cystic, avascular	1993.12	0.4
6	59	M	R	HTN, cerebral infarction	Capsular	2	Inf	wound leakage	MMC (0.2)	−	P	good	cystic, avascular	1994.4	2.0
7	60	F	R	none	POAG	4	Inf	none	MMC (0.1)	−	P	good	cystic, avascular	1994.5	2.2
8	28	M	R	hepatitis	POAG	0	Sup	shallow chamber, corneal epithelial defects	5-FU (50)	+	P	good*	cystic, avascular	1994.5	6.0
9	30	F	R	none	Secondary	1	Sup	wound leakage	MMC (0.2)	−	P	good	cystic, avascular	1995.10	5.0
10	66	M	R	tuberculosis	Secondary	0	Sup	none	MMC (0.1)	−	P	good	cystic, avascular	1995.12	3.0
11	52	M	R	DM	POAG	0	Sup	none	MMC (0.2)	+?	P	good	cystic, avascular	1996.2	3.6

HTN = hypertension; DM = diabetes mellitus; POAG = primary open angle glaucoma; NTG = normal tension glaucoma; Sup = superior; Inf = inferior; 5-FU = 5-fluorouracil; MMC = mitomycin C; P = phakic; A = aphakic;* with topical eyedrops.

Table 5b Summary of cases with bleb related infections

Patient No	Prophylactic use of eyedrops	Bacterial cultures		Antibiotic therapy			Surgery (antibiotics in OIS)	Visual activity		
		Source	Results	Topical	Subconjunctival	Systemic		Pre BRI	Pre therapy	Post BRI
1	none	Bleb surface	no growth	OFLX, GM	GM	IPM/CS, AMK	none	0.1	HM	HM
2	OFLX+steroid	Bleb surface	α streptococcus	OFLX	GM	PIPC, GM, MINO	Lens + Vit (GM)	0.2	LP	NLP
3	none	Bleb surface	no growth	OFLX, SBPC	GM	IPM/CS, SBPC, OFLX	none	0.2	HM	0.03
4	unknown	Bleb surface	no growth	OFLX, SBPC, TOB	AMK	CEZ, CCL	none	0.5	0.01	0.3
5	MCR+steroid	Bleb surface	no growth	OFLX	GM	CTM	none	0.8	0.2	0.8
6	none	unknown	unknown	OFLX, NFLX	none	SBPC, IPM/CS, CXM, LVFX	enucleation	0.4	0.4	NLP
7	OFLX	Bleb surface	*S epidermidis P acnes*	OFLX, SBPC	GM	IPM/CS, CCL	none	0.4	0.1	NLP
8	none	Bleb surface	*P acnes*	OFLX, SBPC	GM	IPM/CS, ASPC, AMK, CTM, PIPC, CPZ, CTZ	PEA+IOL+Vit (GM+PIPC)	1.2	HM	1.2
9	MCR	Bleb surface	no growth	MCR, SBPC	AMK	PIPC, FMOX, AMK	PEA+Vit (GM+PIPC)	0.05	HM	0.05
10	OFLX+steroid	Bleb surface	no growth	OFLX, SBPC	AMK	PIPC, FMOX, AMK	none	0.4	HM	0.3
11	OFLX	Bleb surface	*S equisimilis, S aureus P aeruginosa*	OFLX, SBPC	GM	FMOX, VCM, CCL	none	0.1	0.01	0.1

OIS = ocular irrigating solution; BRI = bleb related infection; NLP = no light perception; LP = light perception; HM = hand movement; OFLX = ofloxacin; NFLX = norfloxacin; LVFX = levofloxacin; MCR = micronomicin; GM = gentamicin; TOB = tobramycin; AMK = amikacin; IPM/CS = imipenem/cilastatin; MINO = minocycline; SBPC = sulbenicillin; PIPC = piperacillin; ASPC = aspoxicillin; FMOX = flomoxef; CEZ = cefazolin; CCL = cefaclor; CTM = cefotiam; CXM = cefuroxime; CPZ = cefoperazone; CTZ = ceftezole; VCM = vancomycin; Lens = lensectomy; PEA = phacoemulsification; IOL = intraocular lens implantation; Vit = vitrectomy.

Table 6 Estimates of bleb related infections by clinical risk factor and the estimated risk of bleb related infection

Clinical factor	*No of cases/No of trabeculectomies*	*Incidence (%)*	*Relative risk*	*p Value*
Side				
Right	9/466	1.93	4.83	0.032
Left	2/500	0.40		
Age (years)*				
<60	8/328	2.43	2.67	0.226
>60	3/304	0.99		
Number of operations				
Initial	7/670	1.04	0.77	0.744
More than one	4/296	1.35		
Lens				
Phakic	10/858	1.17	1.26	>0.999
Aphakic, pseudophakic	1/108	0.93		
Site of trabeculectomy				
Inferior	2/70	2.86	2.84	0.187
Superior	9/896	1.00		
Early postoperative complications				
Corneal epithelial defect	2/87	2.30	2.25	0.260
(−)	9/879	1.02		
Wound leak	3/86	3.99	3.84	0.066
(−)	8/880	0.91		
Shallow anterior chamber	3/220	1.36	1.27	0.720
(−)	8/746	1.07		
Choroidal detachment	1/151	0.66	0.54	>0.999
(−)	10/815	1.23		
Chronic or intermittent bleb leaks (Siedel's test)				
(+)	4/76	5.26	6.69	0.008
(−)	7/890	0.79		
Bleb appearance				
Avascular, hypovascular	11/699	1.57	—	0.041
Others	0/267	—		
Cystic thin walled	11/554	1.99	—	0.003
Others	0/412	—		
Long term topical antibiotic therapy				
(+)	6/638	0.94	0.62	0.523
(−)	5/328	1.52		
Systemic diseases*				
Systemic hypertension	3/154	1.95	0.16	0.734
(−)	8/478	1.67		
Diabetes mellitus	2/65	3.07	1.94	0.315
(−)	9/567	1.59		

*Number of patients.

tomy following diagnostic aqueous and vitreous cultures. Anterior chamber aspiration before antibiotic therapy was performed in one eye (No 9).

The association of each clinical factor with the occurrence of bleb related infection was evaluated by Fisher's exact test. The presence of an early wound leak, a positive Seidel's test, and a thin walled, cystic bleb were significantly associated with the development of bleb related infection (Table 6). Presumed risk factors for bleb related infection, such as the site of the bleb, long term antibiotic therapy, and diabetes mellitus, were not significantly associated with the incidence of bleb related infection. The relative risk of bleb related infection was estimated to be higher than 3.00 in right eye with a bleb, early wound leakage, and a positive Seidel's test (Table 6).

The rates of infection free survival, determined from the Kaplan–Meier survival curve, are illustrated in Figure 1. The survival rates were not significantly different among the three groups (log rank test). As shown in Table 4, there was no difference in the rate of infection as a function of MMC concentration.

Ocular surface cultures were positive in four eyes with more than one organism growing in two eyes: *Propionibacterium acnes*, two eyes; *Staphylococcus epidermidis*, one eye; α streptococcus, one eye; *Staphylococcus aureus*, one eye; *Streptococcus equisimilis*, one eye; and *Pseudomonas aeruginosa*, one eye. Both aqueous and vitreous specimens were obtained for culture from three eyes and the cultures were negative.

Visual acuity improved by more than two lines of the Snellen equivalent after topical and systemic antibiotic therapy in four MMC treated eyes, one 5-FU treated eye, one eye with no adjunctive therapy, and after anterior chamber aspiration and antibiotic therapy in one MMC treated eye. Three patients had a visual acuity loss of two or more lines of the Snellen equivalent.

Scarred, non-functional blebs developed in all three eyes that underwent vitrectomy; one eye became phthisical. Of the seven eyes that did not undergo vitrectomy, five had an intraocular pressure of 20 mm Hg or lower with or without hypotensive treatment, one eye became phthisical, and one eye that underwent a second trabeculectomy with MMC treatment had an intraocular pressure of 20 mm Hg or lower without antiglaucoma medication. The eleventh eye was unsuccessfully treated with antibiotics and was enucleated by a referring ophthalmologist.

Discussion

The success rate of filtering surgery has increased distinctly since the advent of 5-FU or MMC adjunctive treatment. The use of these agents results in better control of postoperative intraocular pressure with less antiglaucoma medication.[2–4 12] Trabeculectomy with antiproliferatives frequently results in the development of an avascular, cystic bleb. Cystic, thin walled blebs are more susceptible to infection than thick walled blebs.[5 6] In the present study, the incidence of bleb related infection in eyes with cystic blebs was higher (p=0.003, Fisher's exact test) than that in eyes with thick walled blebs. The incidence of a positive Seidel's test at the time of the infection was significantly higher in eyes with bleb related infection compared with those without infection (p=0.008, Fisher's exact test); in fact, four of the 11 cases of bleb related infected blebs gave a positive Seidel's test. The findings support the idea that in the presence of an active bleb leak, at the onset of infection, the organisms may penetrate the conjunctival defect overlying the bleb. However, it may be that the organisms must also be able to penetrate the non-leaking conjunctiva overlying the bleb; this idea is supported by the results that seven of the 11 infected eyes did not give a positive Seidel's test. Some organisms produce exotoxins, endotoxins, or other substances that might aid penetration of the bleb[13]; however, the mechanism of penetration through the non-leaking conjunctiva overlying the bleb has not been established. Greenfield and associates suspected that some of the blebs that developed infection gave a negative Seidel's test from being plugged by mucopurulent debris.[14] In patient No 11 we observed a bleb with mucopurulent material attached and that bleb later gave a negative Seidel's test.

The cumulative incidence of bleb related endophthalmitis after trabeculectomy without antiproliferatives ranges from 0.2% to

Table 7 Bleb related infection after trabeculectomy with or without antiproliferatives

Author	*Year*	*Antiproliferatives*	*No of cases*	*No of eyes*	*Incidence (%)*
Freedman	1978	none	2	133*	1.5
Mills	1981	none	2	435	0.45
Shirato	1982	none	1	113	0.9
Katz	1985	none	2	1100*	0.2
Wolner	1991	5-FU	13	229	5.7
			4†	133	3.0
			9‡	96	9.4
Ticho	1993	5-FU	4	105	3.8
			2†	88	2.3
			2‡	17	11.8
Higginbotham	1996	MMC	6	229	2.6
			2†	179	1.1
			4‡	50	8.0
Greenfield	1996	MMC	13	609	2.1
Present study	1997	none	1	76*	1.3
			1†	74	1.4
			0‡	2	0
		5-FU	3	228*	1.3
			3†	210	1.4
			0‡	18	0
		MMC	7	662*	1.1
			5†	612	0.8
			2‡	50	4.0

*Number of trabeculectomies; †superiorly located blebs; ‡inferiorly located blebs; 5-FU = 5-fluorouracil; MMC = mitomycin C.

1.5%.[10 15–17] The incidence of delayed onset, bleb related infection following trabeculectomy with 5-FU treatment is between 3.8%[18] and 5.7%[19] (Table 7). The incidence of delayed onset, bleb related endophthalmitis following trabeculectomy with 5-FU treatment appears to be higher than that for trabeculectomy without 5-FU treatment. In the present study, however, the infection rate was 1.3% after trabeculectomy with 5-FU treatment, which is considerably lower than that found in previous studies. The incidence of bleb related endophthalmitis after trabeculectomy with MMC has been reported by two independent studies to be 2.6% and 3.1%, respectively.[14 20] In contrast, the rate of bleb related infection after trabeculectomy with MMC treatment in our study (1.1%) is lower than that in their study.

To the best of our knowledge, the present study is the first to compare the incidence of delayed onset, bleb related infection after trabeculectomy with either MMC or 5-FU treatment. Trabeculectomy with MMC treatment results in thinner, more cystic, and avascular conjunctival blebs as opposed to that with 5-FU treatment.[8] Therefore, a higher incidence of delayed onset, bleb related infection should be anticipated after trabeculectomy with MMC treatment. In the present study, however, the incidence of infection following trabeculectomy with MMC treatment was similar to that in patients who received 5-FU treatment following trabeculectomy. The true incidence rate per patient year of bleb related infection after trabeculectomy with MMC treatment remains to be clarified, because the follow up period in the present study is not long enough, relative to the patient's lifespan, to draw a definitive conclusion.

Wolner and associates reported that the relative risk for the development of bleb related endophthalmitis after trabeculectomy performed in the inferior quadrants versus that in the superior quadrants with 5-FU treatment was 4.0.[19] Caronia and associates reported an incidence of bleb related infection in trabeculectomies with 5-FU or MMC treatment performed at the inferior limbus of 11.9%.[21] Higginbotham and associates reported bleb related endophthalmitis after trabeculectomy with MMC treatment developed in 8.0% of patients in which an inferior approach was used and in 1.1% of patients in which a superior approach was used.[20] Greenfield and associates reported that bleb associated endophthalmitis developed in five of 38 eyes after inferior quadrant trabeculectomy (13.2%) and in four of 251 eyes after superior quadrant trabeculectomy (1.6%).[14] In the present study, the incidence of bleb related infection after trabeculectomy performed in the inferior quadrant was higher than that after trabeculectomy performed in the superior quadrant (4.0% *v* 0.8%) only in the MMC treatment group; however, the difference was not significant (p=0.092, Fisher's exact test). The discrepancy between the above mentioned reports and the current study might reflect at least partly a racial difference in the tissue response to trabeculectomy. It has been known that the trabeculectomy bleb is more prone to scar down in Japanese people. Yamashita and associates reported that the final success rate in maintaining the intraocular pressure at or below 20 mm Hg after the first trabeculectomy was 60.8% in primary open angle glaucoma for about 5 years.[22] It may be that this also holds even when the antiproliferatives are administered.

Other reported risk factors for the occurrence of bleb related infection were sex and age.[19] Wolner and associates reported that 82% of patients who developed bleb related endophthalmitis were either male or younger than 60 years of age.[19] We were unable to find any sex predilection (six males, five females). However, eight of 11 patients were younger than 60 years of age. Young patients may be more physically active and be more exposed to infectious organisms.

We attempted to determine if the incidence of bleb related infection is related to major postoperative complications—for example, corneal epithelial defects, early wound leakage, shallow anterior chamber, and choroidal detachment. Only early wound leakage was identified as a high risk factor, which supports the idea that thin walled blebs are susceptible to infection.

Non-ocular conditions, such as diabetes mellitus, neoplastic disease for which the patient has received antineoplastic drugs or irradiation, and poor general health,[23 24] may increase the susceptibility of patients to postoperative infection.

It is well known that patients with diabetes mellitus are more likely to develop infections.[25] In the present study, two of 65 patients with diabetes mellitus developed a postoperative bleb related infection, and there were no cases of other systemic conditions that developed a postoperative bleb related infection. It is unknown whether the prophylactic use of postoperative topical antibiotics lowers the incidence of delayed onset, bleb related infection.

In the present study, the long term, topical antibiotic therapy was not related to the incidence of bleb related infection. However, it should be noted that the eyes with thin walled blebs tended to be kept on long term, topical antibiotics. Mandelbaum and associates found that there was no relation between the organisms residing on the conjunctiva and those responsible for the infection in 13 of 18 eyes cultured at the time of active endophthalmitis.[13] In addition, Wand and associates reported long term antibiotic use does not alter the conjunctival flora.[26] Thus, we believe that the routine long term prophylactic use of topical antibiotics is not advisable after trabeculectomy, and that the use of antibiotic eyedrops should be limited to patients with thin walled and leaky blebs.

Bleb related infection is one of the most hazardous complications of glaucoma filtration surgery. It is associated with bleb failure and loss of functional vision and the therapeutic outcome depends heavily upon early detection and treatment. Careful instruction to patients who have undergone trabeculectomy regarding the signs, symptoms, and significance of bleb related infection and the need to seek immediate attention for this potentially blinding infection must be emphasised.

The authors have no proprietary interest in any aspect of this study.

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