Risk Factors for Glaucoma Filtering Bleb Infections

Joern B. Soltau, MD; Robert F. Rothman, MD; Donald L. Budenz, MD; David S. Greenfield, MD; William Feuer, MS; Jeffrey M. Liebmann, MD; Robert Ritch, MD

Methods: A case-control study comparing all consecutive cases of glaucoma filtering bleb-related infections (55 eyes of 55 patients) with matched control eyes between January 1, 1990, and June 30, 1998, was performed. Bleb-related infection was classified as blebitis when a mucopurulent infiltrate was identified within the bleb and associated with mild to moderate anterior segment inflammation. Eyes with endophthalmitis had hypopyon, cells in the anterior vitreous cavity, or a positive vitreous biopsy sampling result. A control was selected for each case based on matching of the surgeon, date and type of glaucoma surgery, and type of antifibrotic agent used. Multivariate, matched, case-control logistic regression analysis was performed using age, race, sex, diagnosis, number of previous incisional operations, filtering bleb location, and presence of bleb leak to determine which variables were associated with bleb-related infection.

Results: The odds of an eye with a bleb-related infection being seen with a concomitant late-onset bleb leak are 25.8 times the odds of a noninfected eye having a late-onset bleb leak at any time in the postoperative period (P<.001; 95% confidence interval, 2.3-294.1). Other risk factors for bleb-related infection included younger age (P = .05), black race (P = .03), diagnosis of primary open-angle glaucoma (P = .03), and inferior location of the filtering bleb (P = .04).

Conclusions: Late-onset bleb leakage is a significant risk factor for bleb-related infection. The risk of infection may warrant closure of late-onset bleb leaks in selected eyes.

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GAUCOMA filtering surgery is commonly performed to control intraocular pressure (IOP) when medical therapy or laser trabeculoplasty fail to do so. Associated with this procedure, however, is a small, but significant, risk of late-onset bleb-related infection. Previously documented risk factors for bleb-related infection include use of antifibrotic agents in conjunction with filtering surgery1-3 and inferior location of the filtering bleb.4-7 Because the conjunctiva and sclera provide the main barriers against entry of infectious organisms into the eye, disruption of these barriers due to glaucoma filtering surgery, combined with a leak in the conjunctival filtering bleb, may be an additional risk factor. In fact, the tear film, which contains bacteria known to harbor organisms capable of causing endophthalmitis,8,10 has been shown to have direct access to the anterior chamber via a leaking filtering bleb.11 Several researchers5,6,12-14 have proposed a correlation between late-onset bleb leaks and bleb-related infections. However, these studies are limited by the absence of a control group. We performed a case-control study to further assess late-onset bleb leak and other clinical variables as risk factors for bleb-related infection.

RESULTS

A total of 110 eyes of 110 patients (55 cases and 55 controls) were included in the study. Six different surgeons were responsible for the operations in all patients. The patient demographic and clinical characteristics are summarized in Table 1. There was a higher proportion of men in the bleb-related infection group. There were no differences in glaucoma diagnosis, number of previous operations, type of most recent filtering surgery, and location of filtering bleb between the 2 groups. Of the 55 eyes, a trabeculectomy alone was performed in 50 (91%), while a trabeculectomy combined with cataract extraction and lens implantation was performed in 5 (9%) (phacoemulsification, 3 [5%]; and manual extracapsular cataract extraction,
PATIENTS AND METHODS

After approval by the institutional review boards at each institution, the medical records of all patients who had late-onset bleb-related infection (>1 postoperative month) between January 1, 1990, and June 30, 1998, were reviewed. All patients had undergone trabeculectomy, either alone or combined with cataract extraction and intraocular lens implantation. If both eyes had a bleb-related infection during the follow-up, only the right eye was enrolled. If the enrolled eye had more than 1 bleb-related infection, the first episode was used as the bleb-related infection in the study. Data abstracted from the medical record included demographics, glaucoma diagnosis, date and type of glaucoma filtering surgery, filtering bleb location, surgeon, type of antifibrotic agent, and number of previous ocular operations. Visual acuity, IOP, concurrent antiglaucoma medication, and documentation of a bleb leak were recorded for the visit before bleb-related infection diagnosis and date of presentation. The technique for assessing a bleb leak was as follows. Under cobalt blue slitlamp illumination, a moistened fluorescein strip was used to paint the bleb surface. A bleb leak was defined as a spontaneous focal point source of aqueous leakage from an area of interrupted conjunctival tissue occurring more than 1 month postoperatively. Patients with diffuse transconjunctival aqueous flow but a negative result on the Seidel test were not considered to have an actual bleb leak.

Bleb-related infection was classified as blebitis when a mucopurulent infiltrate was identified within the bleb and associated with mild to moderate anterior segment inflammation. An example of a patient with blebitis is shown in the Figure. Patients who were seen clinically with blebitis, but subsequently had negative culture results, were excluded. If a hypopyon was present, cells were reported in the anterior vitreous cavity, or if aqueous or vitreous humor biopsy cultures were positive, the infection was categorized as endophthalmitis. Because of the low yield of anterior chamber and vitreous cultures in patients with endophthalmitis, patients with the clinical signs of endophthalmitis previously described but with negative culture results were included. Bleb leaks were only counted as associated with an infection in the cases if they were noted at the visit when, or the visit before, the infection was diagnosed.

Controls were matched by surgeon, type of surgery, and type of antifibrotic agent used. The control that fit all of the matching criteria and was closest to the date of surgery in the case was used. Best-corrected visual acuity, IOP, filtering bleb location, and concurrent antiglaucoma medication were recorded. Since there was only 1 patient with a bleb in the nasal portion of the eye, this location was combined with inferior location for the sake of data analysis. The entire available follow-up was used to search for evidence of a Seidel test–positive bleb leak and counted if a leak was noted at any time after the first postoperative month. If not available in the patient’s medical record, follow-up data were obtained by calling the patient’s referring ophthalmologist.

Continuous variables were compared with the 2-sided t test unless otherwise noted, while categorical variables were compared with the exact χ² test or the Fisher exact test. A matched case-control logistic regression analysis was performed to determine which variables were predictors of bleb-related infection. Other variables analyzed as part of the logistic regression analysis included age, race, sex, number of prior incisional operations, filtering bleb location, and glaucoma diagnosis. Data analysis was performed using a commercially available statistical program (SPSS for Windows, release 7.5; SPSS Inc, Chicago, Ill).

2 [4%]). An antifibrotic agent was used in all cases. Fluorouracil was used in 24 (44%) and mitomycin in 31 (56%) of the eyes in each group. Since the type of surgery and antifibrotic agent were used as part of the matching criteria, the number of patients was the same in each group for these variables. The date of surgery was successfully matched to within 2 months in all case-control pairs.

Bleb-related ocular infection occurred a mean ± SD of 25.1 ± 22.7 months after the surgery (median, 19.9 months; range, 1-96 months). Blebitis occurred in 24 (44%) and endophthalmitis in 31 (56%) of the cases. No leaks were observed in 29 (53%) of the case-control pairs, and in both the case and the control in 3 (5%) of the pairs. A leak was observed in the case but not the control 38% of the time and in the control but not the case 4% of the pairs. Blebs were observed in 29 (53%) of the case-control pairs, (44%) and endophthalmitis in 31 (56%) of the cases. No blebs were observed in 29 (53%) of the case-control pairs, and in both the case and the control in 3 (5%) of the pairs.

Visual acuity outcomes are given in Table 3. Eyes in the bleb-related infection group had a significantly lower visual acuity at the final follow-up than controls. Eyes with endophthalmitis had a lower final median visual acuity than those with blebitis, although the difference did not reach statistical significance. Table 4 provides the results of univariate and multivariate logistic regression for various risk factors for bleb-related infection. After adjusting for age, sex, race, number of previous operations, type of glaucoma, and location of the filtering bleb, a bleb leak was still a significant pre-

An infected filtering bleb in a 71-year-old man 4 years after a trabeculectomy was performed with mitomycin. There is pus emanating from a hole in the conjunctival filtering bleb. Cultures of this material were positive for Staphylococcus aureus.
Table 1. Demographic and Clinical Characteristics*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eyes With Bleb-Related Infection</th>
<th>Control Eyes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>60 ± 21</td>
<td>66 ± 18</td>
<td>.11</td>
</tr>
<tr>
<td>Male sex</td>
<td>35 (64)</td>
<td>23 (42)</td>
<td>.04</td>
</tr>
<tr>
<td>Black race</td>
<td>14 (26)</td>
<td>6 (11)</td>
<td>.08</td>
</tr>
<tr>
<td>Glaucoma diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary open angle</td>
<td>37 (67)</td>
<td>32 (59)</td>
<td></td>
</tr>
<tr>
<td>Chronic angle closure</td>
<td>4 (7)</td>
<td>7 (13)</td>
<td>.72</td>
</tr>
<tr>
<td>Pseudodiscission</td>
<td>4 (7)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Other†</td>
<td>10 (18)</td>
<td>12 (22)</td>
<td></td>
</tr>
<tr>
<td>No. of previous incisional operations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>26 (47)</td>
<td>30 (56)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23 (42)</td>
<td>18 (33)</td>
<td>.65</td>
</tr>
<tr>
<td>2-3</td>
<td>6 (11)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Location of filter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior</td>
<td>36 (66)</td>
<td>40 (73)</td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>18 (33)</td>
<td>15 (27)</td>
<td>.53</td>
</tr>
<tr>
<td>Nasal</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

* Data are given as the number (percentage) in the specific category and group. Some percentages do not total 100% because of rounding.  
† Pigmentary neovascular, traumatic, and juvenile open-angle glaucoma.

Table 2. Intraocular Pressure (IOP) and Glaucoma Medications*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Eyes With Bleb-Related Infection</th>
<th>Control Eyes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP, mm Hg</td>
<td>10.4 ± 4.9</td>
<td>13.9 ± 6.7</td>
<td>.005</td>
</tr>
<tr>
<td>No. of glaucoma medications</td>
<td>0.11 ± 0.40</td>
<td>0.41 ± 0.80</td>
<td>.04</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD.

Table 3. Final Visual Acuity (VA) Outcomes  

<table>
<thead>
<tr>
<th>VA</th>
<th>Group</th>
<th>Median</th>
<th>Range†</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes with bleb-related infection</td>
<td>20/100</td>
<td>20/20-NLP</td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Control eyes</td>
<td>20/50</td>
<td>20/20-NLP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes with blebitis</td>
<td>20/80</td>
<td>20/25-2/200</td>
<td></td>
<td>.06</td>
</tr>
<tr>
<td>Eyes with endophthalmitis</td>
<td>20/200</td>
<td>20/20-NLP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* NLP indicates no light perception.  
† Mann-Whitney test.

dictor of infection. In the multivariate analysis, the odds that patients in the bleb-related infection group would have a leak were 25.8 times the odds that patients in the control group would have a leak. In 7 of the 21 cases, a leak was noted before the visit when bleb-related infection was diagnosed, with no leak observed during similarly timed visits in the corresponding controls; on the other hand, a leak was noted in 1 control patient before the visit when bleb-related infection was diagnosed. This difference in the rate of leaks noted before infection approached statistical significance (P = .07, exact McNemar test).

Other variables in the multivariate analysis that were found to be risk factors for bleb-related infection, although not as strong, included younger age at the time of surgery, black race, and inferior or nasal bleb location. Patients in the control group were followed up for an additional average of 28.0 months to identify bleb leaks occurring later than the date of their infection. The mean ± SD total average follow-up for the control group was 53.1 ± 31.9 months (median, 46.8 months; range, 3.0-163.0 months).

The increase in success of trabeculectomy associated with the use of antifibrotic agents may put patients at an increased risk of late-onset complications, including bleb-related ocular infection1-3 and late-onset filtering bleb leaks.12-20 Several studies4,6,12-14 have suggested a relation between these 2 complications. The present study, which is the first, to our knowledge, to use a control group, found that bleb leaks are associated with bleb-related infection. Although a causal relation cannot be drawn based on this retrospective study, the strong association between late-onset bleb leaks and bleb-related infection suggests that these 2 factors are related. Several researchers have questioned which comes first, the bleb leak or the infection. It seems more plausible that the disruption of the main barriers to infection in the eye wall (the sclera and the conjunctiva) provides an easier access for the bacteria-rich tear film10,11 rather than the bacterial pathogen creating a hole in the conjunctiva. Only a long-term prospective study could answer this question definitively.

Late-onset leaks are more common after full-thickness procedures compared with trabeculectomy without antifibrotic agents.21 Trabeculectomies performed with fluorouracil1 appear to have a higher rate of late-onset bleb leaks than trabeculectomies performed without fluorouracil.16,17 and trabeculectomies performed with mitomycin may have an even higher rate of late-onset bleb leaks than those performed with fluorouracil.18,20 The frequency of late-onset filtering bleb leaks seems to be increasing, possibly due to increased use of these antifibrotic agents.22,23 Histopathologic examination of blebs after trabeculectomy with mitomycin reveals irregularities in the conjunctival epithelium, breaks in the basement membrane, and conjunctival and subconjunctival hypocellularity, each of which may predispose to bleb leaks.24-27 Belyea et al18 retrospectively reviewed 385 consecutive eyes undergoing trabeculectomy with fluorouracil or mitomycin and reported a 1.8% overall incidence of late-onset sequential multifocal leaks. The histopathologic features of 3 eyes demonstrated epithelial breakdown, hypocellularity, and stromal collagen necrosis in the bleb.

The present study attempted to identify bleb leaks by retrospective review, thus introducing the possibility of underreporting bleb leaks. A patient with a bleb-related ocular infection probably undergoes closer examination of the bleb than an asymptomatic patient. To attempt to overcome underreporting of bleb leaks, we continued to look for evidence of late-onset bleb leaks for an additional average of 28 months in the control group to increase the chances of identifying a bleb leak. We also used the presence of a leak at any time during follow-up.
in the control group compared with the presence of a leak at or immediately before the visit when bleb-related infection was diagnosed in the cases, to err on the side of overestimating the number of bleb leaks in the control group. Despite this conservative approach, the association between bleb leak and bleb-related infection was significant. In a cross-sectional prospective study looking at late-onset bleb leaks, Greenfield et al.20 found an incidence of 2.9%, similar to the 4% found in the control group in the present study. This similarity suggests that the control group was adequately screened for bleb leaks and that underreporting was not an issue.

In the present study, an antifibrotic agent was used in all eyes. The type of antifibrotic agent used was part of the matching criteria. Katz et al.19 in a retrospective study, reported that 2 (11%) of 19 eyes had late-onset bleb leaks after trabeculectomy with fluorouracil compared with 1 (5%) of 20 eyes after trabeculectomy with mitomycin. Belyea et al.18 reported a slightly greater, yet statistically insignificant, rate of late-onset leaks after filtering surgery with fluorouracil (2.6%) compared with 1 (5%) of 20 eyes after trabeculectomy with mitomycin (1.0%). However, in 2 prospective studies,18,20 a higher incidence of late-onset bleb leaks was found after trabeculectomy with mitomycin. In fact, Greenfield et al.20 found that bleb leaks occurred 3 times more often following trabeculectomy with mitomycin than fluorouracil. A significant percentage, if not most, of glaucoma filtering surgery is performed with antifibrotic agents,28 and the number of late-onset bleb leaks will likely be underestimated if the overestimating the number of bleb leaks in the control group at the same time postoperatively. One possible explanation for the lower IOP in the group that developed infections is that this group had a higher incidence of bleb leaks, which cause hypotony. Greenfield et al.20 found that, in contrast with early-onset bleb leakage, many eyes with late-onset leaks had a normal IOP and elevated blebs.

Since one of the matching criteria for this study was type of surgery, this study does not address whether trabeculectomy alone vs trabeculectomy combined with cataract surgery predisposes to bleb-related infection. However, of the 55 patients in the case group, only 5 (9%) had undergone combined cataract filtering surgery. Greenfield et al.20 found that bleb leakage was uncommon after combined glaucoma and cataract surgery. Others29-31 have reported low rates of leakage after combined procedures. This is consistent with the infrequent development of hypotonia and late endophthalmitis following combined cataract and glaucoma surgery and may reflect the thicker bleb walls present in these eyes.6,32 Greenfield et al.20 also found that thin-walled blebs were more prone to leakage than diffuse blebs with thicker walls.

Wolner et al.2 found a relatively high proportion of men with bleb-related endophthalmitis compared with women. Male sex was found to be a risk factor for bleb-related infection in the present univariate analysis, but the multivariate analysis did not confirm this association. Several studies3-7 have shown an increased risk of bleb-related endophthalmitis in blebs located at the inferior limbus, possibly related to exposure of the bleb to the bacteria-rich tear film. In the present study, this association was confirmed in a multivariate analysis.

It is critically important to educate patients about the possible lifelong risk, symptoms, and signs of bleb-related infection and to routinely check for leaks in functioning filtering blebs to identify eyes at high risk for acquiring an infection. Closing late-onset filtering bleb leaks is challenging, and definitive indications have not yet been established. Previous bleb-related infection, monocular patients, and decreased vision secondary to hypotony (corneal folds, maculopathy, a shallow or flat anterior chamber, or chronic choroidal effusions) may be indications for closing late-onset filtering bleb leaks. A multitude of nonsurgical methods for closing late-onset bleb leaks, including aqueous suppressants, pressure patching, oversized contact lenses, argon laser therapy, autologous blood injections, cyanoacrylate and fibrin glue, and compression sutures, have been used.33-34 When these conservative methods fail, conjunctival advancement or autografts32,45 have been shown to be successful.

The development of bleb-related infection as a longterm complication of glaucoma filtering surgery is clearly

### Table 4. Risk Factor Analysis

<table>
<thead>
<tr>
<th>Variable *</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Glaucoma diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POAG vs CAGG</td>
<td>0.5 (0.1-2.1)</td>
<td>.59</td>
<td>0.3 (0.02-3.4)</td>
<td>.03</td>
</tr>
<tr>
<td>POAG vs PXG</td>
<td>1.0 (0.2-5.1)</td>
<td></td>
<td>2.9 (0.3-25.3)</td>
<td></td>
</tr>
<tr>
<td>POAG vs other</td>
<td>0.6 (0.2-1.9)</td>
<td>.31</td>
<td>0.02 (&lt;0.01-0.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Inferior or nasal bleb</td>
<td>1.7 (0.8-4.7)</td>
<td></td>
<td>7.0 (1.9-50.7)</td>
<td></td>
</tr>
<tr>
<td>Univariate Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate Analysis†</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* POAG indicates primary open-angle glaucoma; CAGG, chronic angle-closure glaucoma; and PXG, pseudoexfoliation.
† All variables included in the logistic regression model.
‡ For a 10-year increment in age.
multifactorial. Not all patients with late-onset bleb leaks develop bleb-related infection, and not all patients with bleb-related infection have a definite leak documented beforehand, or at the time of, infection. Other factors, including bleb wall thickness, bleb location, presence of blepharitis, and presence of pathogenic bacteria, on the ocular surface may also be important. To our knowledge, this report is the first to demonstrate bleb leak as a significant risk factor for ocular infection using a case-control design. Limitations, including small sample size and retrospective design, preclude generalized recommendations for leak management in all eyes. However, based on these data, we recommend closure of leaking filtering blebs in patients who are thought to have a significant threat to vision from potential bleb-related infection.

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REFERENCES