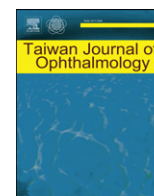


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Review article

Bleb-related infection: Clinical features and management

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ABSTRACT

Bleb-related infection is a potentially sight-threatening complication of glaucoma filtration surgery. Here, we describe its clinical features and management. Blebitis, or stage I infection, is a mild form of bleb-related infection. The prognosis of blebitis is usually good, unless it has progressed to later stages. Endophthalmitis, or stage II or stage III infection, however, is a much-advanced stage of the infection and has a poorer prognosis. For treatment of bleb-related infections, immediate intensive antibacterial treatment is urgently required.

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1. Introduction

Filtration surgery is widely employed for medically uncontrolled glaucoma. With the introduction of antimetabolites such as mitomycin C and 5-fluorouracil, the success rate of filtration surgery has much increased.¹ However, several types of late-onset complications still develop in a significant number of cases, which should be of concern to both patients and ophthalmologists. One of these is bleb-related infection² in which bacteria invade through the filtering bleb and then through the functioning fistula between the bleb and the anterior chamber, and finally into the intraocular tissues. This is a serious complication that can lead to permanent visual impairment. Bleb-related infection develops in the majority of cases after trabeculectomy and has become much more common due to the popularity of this procedure, but it may arise after any type of filtration surgery. Here, we discuss the clinical features, incidence, and management of this often serious complication of glaucoma surgery.

2. Clinical features

2.1. Classification

Bleb-related infections are classified into blebitis and endophthalmitis. In the former, the infection is located predominantly in the filtering bleb itself whereas, in the latter, the main locus of the

infection is inside the eyeball. All bleb-related infections start as a form of blebitis, but not all cases present as blebitis due to its often-rapid progression to endophthalmitis. Approximately 50% of cases are diagnosed as blebitis and 50% as endophthalmitis. Studies by Azuara-Branco and Katz,³ and by Greenfield,⁴ divided endophthalmitis into two stages: one characterized by infection mainly in the anterior chamber and the other involving infection in the vitreous and retina. They proposed a new classification system of bleb-related infection: stage I for blebitis (Fig. 1), stage II for endophthalmitis mainly involving the anterior chamber (Fig. 2), and stage III for endophthalmitis involving the vitreous (Fig. 3). The Japan Glaucoma Society further subdivided stage III into stage IIIa (mild vitreous involvement) and stage IIIb (marked vitreous involvement).⁵ This stage III subclassification is chiefly based on the visibility of the fundus and vitreous opacity detected by B-mode echography. The subclassification is helpful in determining the initial therapy for stage III infection.

2.2. Signs and symptoms

Bleb-related infection begins with conjunctival hyperemia, discharge, foreign body sensation, etc., similar to bacterial conjunctivitis. The bleb shows a purulent, yellowish appearance in stage I, but the anterior chamber is clear, very few cells are present, and there is little or no visual impairment. By contrast, stage II is characterized by a definite flare, with cells possibly apparent in the anterior chamber and hypopyon. Definitive stage III requires vitreous involvement, which may be mild in the earlier stage (stage IIIa), as determined by B-mode echography, but rapidly progresses to the more advanced stage (stage IIIb) unless appropriately treated

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Fig. 1. Stage I bleb-related infection or blebitis. Mild conjunctival hyperemia is present.

(Table 1). With the progression of the infection, intolerable ocular pain and severe visual impairment will usually develop.

2.3. Risk factors

Several risk factors are known to be associated with the development of bleb-related infection.^{6–11} These include eyes operated adjunctively with antimetabolites, bleb leakage present or a positive Seidel test, inferiorly located blebs, avascular blebs, thin-walled blebs, axial myopia, prolonged use of antibiotics, seasons, history of intraocular surgeries, etc. An inferiorly located bleb is associated with a 4- to 8-fold higher incidence of bleb-related infections in eyes adjunctively treated with antimetabolites. Avascular, thin-walled blebs, characteristic of antimetabolite-assisted surgery, are associated with a significantly higher risk for bleb-related infection. Bleb leakage ascertained by Seidel testing is a significant risk factor. Both an apparent leakage and an oozing leakage should be considered a dangerous complication.

2.4. Bacteriological examinations

Bacteriological examinations are essential for appropriate treatment of all bleb-related infections, and conjunctival scraping should be done for blebitis. Intracameral or intravitreal tapping

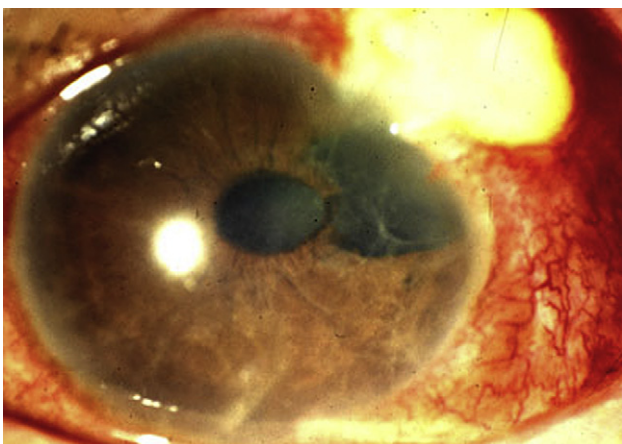


Fig. 2. Stage II bleb-related infection. Conjunctival hyperemia, purulent bleb, and fibrin formation are visible.



Fig. 3. Stage III bleb-related infection. Thick opacity is detected by B-mode echography.

should be performed to identify the causative agents for endophthalmitis cases, i.e., stage II or stage III infection. If intravitreal tapping was properly performed, one can expect cases to be 55–97% culture-positive.^{12–14} The rate of positive cultures increases as the stage progresses.

Although a variety of bacteria may be isolated by culturing, these bacteria may not be the causative agents. Furthermore, the type of bacteria varies across the stages. Gram-positive bacteria are the major isolates, with *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Corynebacterium*, and *Streptococcus* commonly found in stage I infection. Stages II and III are most often associated with *Staphylococcus* and *Streptococcus*, and *Streptococcus* and *Enterococcus*, respectively.

For all isolates, antimicrobial susceptibility should be determined and the most potent antibiotic agent should be used to address the infection.

2.5. Prognosis

The prognosis of a bleb-related infection depends primarily upon its stage and the virulence of the causative bacteria. The prognosis of a stage I infection is generally good with most patients maintaining visual acuity and intraocular pressure (IOP) in the preinfection range. A stage II infection is somewhat worse, but patients can maintain visual acuity and IOP control in many of the cases, unless they progress to stage III. The prognosis of a stage III infection is significantly worse, with visual acuity potentially dropping to the level of hand motion or less, and loss of IOP control, in approximately half of all cases. Some stage III cases ultimately may progress to phthisis bulbi or require enucleation.

Any bleb-related infection caused by *Streptococcus*, coagulase-positive *Staphylococcus*, or Gram-negative bacteria has a poor visual

Table 1
Staging of bleb-related infection.

Stage	Location of infection	Clinical features	Bacterial culture
I	Bleb	Hyperemia, yellowish bleb	Conjunctiva, discharge
II	Anterior chamber	I & cells in anterior chamber hypopyon (occasionally)	Aqueous humor
IIIa	Vitreous	II & vitreous opacity (mild)	Vitreous humor
IIIb	Vitreous	II & vitreous opacity (marked)	Vitreous humor

Table 2
Management of bleb-related infection adopted from the Collaborative Bleb-related Infection Incidence and Treatment Study.⁵

Stage I
—Levofloxacin 0.5% & cefmenoxime 0.5% eye drops, Q 1 h
—Ofloxacin ophthalmic ointment at bedtime
—Subconjunctival injection of vancomycin (25 mg) & ceftazidime (100 mg)
Stage II
—Levofloxacin & cefmenoxime eye drops, Q 1 h
—Ofloxacin ophthalmic ointment at bedtime
—Intracameral injection of vancomycin (1 mg) & ceftazidime (2.25 mg)
—Systemic antibiotics if necessary
Stage IIIa
—Levofloxacin & cefmenoxime eye drops, Q 1 h
—Ofloxacin ophthalmic ointment at bedtime
—Intravitreal injection of vancomycin (1 mg) & ceftazidime (2.25 mg)
—Systemic antibiotics
—Corticosteroid, either systemic or local, may be used after sufficient antibiotic therapy
Stage IIIb
—Levofloxacin & cefmenoxime eye drops, Q 1 h
—Ofloxacin ophthalmic ointment at bedtime
—Immediate vitreous surgery with intravitreal irrigation of vancomycin (100 mg/500 mL) & ceftazidime (200 mg/500 mL)
—Systemic antibiotics
—Corticosteroid, either systemic or local, may be used after sufficient antibiotic therapy

prognosis in most cases, whereas those caused by *S. epidermidis* have a much better prognosis.

3. Incidence

There are several reports on the incidence of bleb-related infection. The Collaborative Bleb-related Infection Incidence and Treatment Study,⁵ a prospective study on bleb-related infection being conducted by the Japan Glaucoma Society, has determined that the probability of bleb-related infection following filtering surgeries with adjunctive mitomycin C was $1.5 \pm 0.6\%$ (cumulative probability \pm standard error) at the 2.5-year follow-up. They also found no correlation with the type of conjunctival incision and that bleb leakage was significantly related to the incidence. According to other investigators, the incidence associated with trabeculectomy is 0.2–0.5% without the use of antimetabolites,^{15,16} 1.9–13.0% for eyes treated with 5-fluorouracil in cases with follow-up of 1–12 years,^{6,17,18} and 1.5–13.8% in cases using intraoperative mitomycin C followed for 16 months to 8 years.^{2,19–22}

4. Management

Immediate intensive treatment is urgently required for all bleb-related infections. Generally, prompt diagnosis and staging is the first course of action, followed by an expeditious bacterial culture. This is followed by antibacterial therapy comprising a combined therapy of eye drops, ointment, subconjunctival or intraocular injection of antibiotics, and systemic antibiotic therapy. Additionally, vitreous surgery is recommended when vitreous involvement is apparent or aggravated. Corticosteroid, either systemic or local, may be used after sufficient antibiotic therapy in cases of stage III progression. The Collaborative Bleb-related Infection Incidence and Treatment Study has employed a predetermined management protocol for bleb-related infection (Table 2).⁵

Patients should be monitored closely. If the ocular condition becomes worse, appropriate measures should be promptly taken. This includes additional administration of antibiotics, confirmation of the antimicrobial spectrum of the current therapy, a change of the antibiotics if needed, and emergency vitreous surgery.

5. Preventive measures

There are several considerations for the prevention of bleb-related infection. Long-term use of antibiotics changes the flora of the conjunctival bacteria and brings new antibiotic-resistant bacteria into existence. Thus, long-term use of antibiotics is not recommended. Jampel et al¹⁰ pointed out that the history of usage or present use of antibiotics over 4 weeks after surgery was a significant risk factor for bleb-related infection. As stated above, some conditions are known to be associated with the development of bleb-related infection: conjunctival leakage, inferiorly located blebs, etc. In such cases, the preventive use of antibiotics might be considered, but usually only for a short period.

Patient education is another important consideration. Information on bleb-related infection reduces the risk of infection by patients' changes in habit and lifestyle, and may also decrease the risk of poor visual prognosis because patients are more careful with ocular hygiene and are more likely to seek prompt consultation if they notice a sign of infection. Periodical consultation with ophthalmologists is also important. For example, short-term use of antibiotic therapy might be recommended when conjunctival leakage is found at consultation.

6. Summary

Bleb-related infection is a potentially sight-threatening complication of glaucoma filtration surgery. Its clinical features and management have been described here.

References

- Chen CW. Enhanced intraocular pressure controlling effectiveness of trabeculectomy by local application of mitomycin-C. *Trans Asia Pacific Acad Ophthalmol* 1983;**9**:172–7.
- 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**:877–83.
- Azuara-Branco A, Katz LJ. Dysfunctional filtering blebs. *Surv Ophthalmol* 1998;**43**:93–126.
- Greenfield DS. Bleb-related ocular infection. *J Glaucoma* 1998;**7**:132–6.
- Yamamoto T, Kuwayama Y. The 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**:453–8.
- Ticho U, Ophir A. Late complications after glaucoma filtering surgery with adjunctive 5-fluorouracil. *Am J Ophthalmol* 1993;**115**:506–10.
- Hori N, Mochizuki K, Ishida K, Yamamoto T, Mikamo H. Clinical characteristics and risk factors of glaucoma filtering bleb infections. *J Jpn Ophthalmol Soc* 2009;**113**:951–63.
- Softau JB, Rothman RF, Budenz DL, Greenfield DS, Feuer W, Liebmann JM, et al. Risk factors for glaucoma filtering bleb infections. *Arch Ophthalmol* 2000;**118**:338–42.
- Matsuo H, Tomidokoro A, Suzuki Y, Shirato S, Araie M. Late-onset transconjunctival oozing and point leak of aqueous humor from filtering bleb after trabeculectomy. *Am J Ophthalmol* 2002;**133**:456–62.
- Jampel HD, Quigley HA, Kerrigan-Baumrind LA, Melia BM, Friedman D, Barron Y, et al. Risk factors for late-onset infection following glaucoma filtration surgery. *Arch Ophthalmol* 2001;**119**:1001–8.
- 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**:570–4.
- Mandelbaum S, Forster RK, Gelender H, Culbertson W. Late onset endophthalmitis associated with filtering blebs. *Ophthalmology* 1985;**92**:964–72.
- Ciulla TA, Beck AD, Topping TM, Baker AS. Blebitis, early endophthalmitis, and late endophthalmitis after glaucoma-filtering surgery. *Ophthalmology* 1997;**104**:986–95.
- Kangas TA, Greenfield DS, Flynn Jr HW, Parrish II RK, Palmberg PF. Delayed-onset endophthalmitis associated with conjunctival filtering blebs. *Ophthalmology* 1997;**104**:746–52.
- Freedman J, Gupta M, Bunke A. Endophthalmitis after trabeculectomy. *Arch Ophthalmol* 1978;**96**:1017–8.
- Katz LJ, Cantor LB, Spaeth GL. Complications of surgery in glaucoma: early and late bacterial endophthalmitis following glaucoma filtering surgery. *Ophthalmology* 1985;**92**:959–63.

17. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the fluorouracil filtering surgery study. *Am J Ophthalmol* 1996;**121**:349–66.
18. 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**:458–65.
19. Greenfield DS, Suñer IJ, Miller MP, Kangas TA, Palmberg PF, Flynn Jr HW. Endophthalmitis after filtering surgery with mitomycin. *Arch Ophthalmol* 1996;**114**:943–9.
20. Shigeeda T, Tomidokoro A, Chen YN, 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**:195–9.
21. Sharan S, Trope GE, Chipman M, Buys YM. Late-onset bleb infections: prevalence and risk factors. *Can J Ophthalmol* 2009;**44**:279–83.
22. 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**:297–300.