Chapter

Post-Operative Infections Following Glaucoma Drainage Surgery

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Abstract

Glaucoma drainage surgery is performed commonly throughout the world for the surgical treatment of glaucoma. Typically, a guarded fistula is fashioned leading to a drainage bleb that represents subconjunctival collection and egress of aqueous humour from the eye. Bleb related infections (BRI) include blebitis and bleb related endophthalmitis (BRE). Although rare, BRI can be blinding, and appropriate vigilance is needed to ensure prompt diagnosis and treatment to save sight. Preoperatively, blepharoconjunctivitis must be treated as well as any potential sources of infection. Clinicians must examine thoroughly to exclude bleb leaks and conjunctival erosions post-operatively. Patients must be educated about seeking care immediately if ocular redness, pain, discharge, or decreased vision develops. If BRI is diagnosed, sampling of ocular tissues is necessary for culture and sensitivity, followed by administration of broad-spectrum antibiotics. The interval from onset of symptoms to treatment, initial visual acuity, clarity of cornea at presentation, type of infecting organism, and presence or absence of diabetes mellitus are associated with final visual outcome particularly for BRE.

Keywords: glaucoma drainage surgery, blebitis, endophthalmitis, micro-organisms, antibiotics, vitrectomy

1. Introduction

Trabeculectomy with antimetabolites is the most commonly performed glaucoma surgery worldwide [1], being indicated for cases of progressive optic neuropathy despite maximum medical therapy. Other forms of drainage surgery include glaucoma drainage device (GDD) implantation, XEN45 gel stent, microshunt implantation and non-penetrating glaucoma surgery such as deep sclerectomy (DS).

Bleb-related infections (BRI), although rare can be very aggressive with poor prognosis and variable response to antimicrobial therapy. BRI includes blebitis and endophthalmitis, which may represent a continuum of infection. Early onset BRI occurs within 1 month of surgery and late onset BRI is defined as occurring after 1 month.

Several studies have addressed the possible risk factors associated with BRI and new surgical techniques have been developed to improve safety. In this chapter, we will discuss the risk factors for BRI following trabeculectomy, the pathogens involved, the treatment protocol and antimicrobial agents that are typically used in treatment.

2. Incidence

The incidence of BRI is difficult to determine because of variable modes and times of presentation. Long-term studies are useful in ascertaining the lifetime risk of BRI, which is important to discuss with patients as part of the informed consent process.

In the Collaborative Initial Glaucoma Treatment Study, the 5-year risk of blebitis and bleb related endophthalmitis (BRE) was 1.5% and 1.1%, respectively [2]. In the Tube Versus Trabeculectomy Study, [3] the 5-year incidence of BRI following trabeculectomy was 4.8% (n = 105). A 20-year study (n = 460) reported cumulative probabilities of blebitis and BRE of 2% and 5%, respectively [4].

In the trabeculectomy versus tube trial, at 5 years, blebitis and endophthalmitis occurred in 1% and 4.8% of cases in the tube and trabeculectomy groups, respectively, but this was not statistically significant [3]. In a large case series of GDD implantations, exposed implants were more likely to be associated with infection than the group generally (16% v 1%), and exposed inferior GDD had a higher rate of infection compared to superior y placed GDD (47% v 8%) [5]. Multiple studies have shown a higher rate of endophthalmitis in patients younger than 18 years of age [6]. Removal of GDD in the clinical setting of BRI is controversial but recommended by the author once the infection has been treated.

The reported rate of BRI after various nonpenetrating surgeries has been 0–1.6% [7–10]. Cases of BRI in this setting usually occur after laser goniopuncture [10]. In a large case series (n = 199) with relatively short follow-up there was 1 case of late onset endophthalmitis following XEN 45 gel stent implantation [11]. Apart from this, there have been a few case reports of BRE following XEN 45 implantation [12–15]. In the author's experience, after 5 years of follow up of 90 eyes implanted with XEN45 gel stent, there were no cases of BRI (unpublished data). One case of BRE has been reported following bleb needling in an eye implanted with microshunt [16].

3. Symptoms and signs of bleb related infection

BRI can lead to severe and permanent loss of vision if not detected and treated in a timely and directed manner. Early on there may be mild signs similar to viral or bacterial conjunctivitis, leading to a delay in seeking medical attention. Cases typically present with a painful red eye, often associated with discharge, eyelid swelling, photophobia, and reduced vision. There may be a prodromal history of headache, conjunctivitis, blepharitis, and coryza [17].

The findings include a milky bleb appearance due to a mucopurulent infiltrate. There is usually swelling and hyperaemia of the conjunctiva with upper eyelid oedema. These findings are known as a "white on red" appearance (**Figure 1**). The anterior chamber may be shallow if there is a bleb leak. Later on, an anterior chamber inflammatory reaction occurs, and anterior vitritis.

Generally, BRE and blebitis present similarly, but the symptoms and signs in BRE are more fulminant with greater reduction in vision and a more accelerated course.

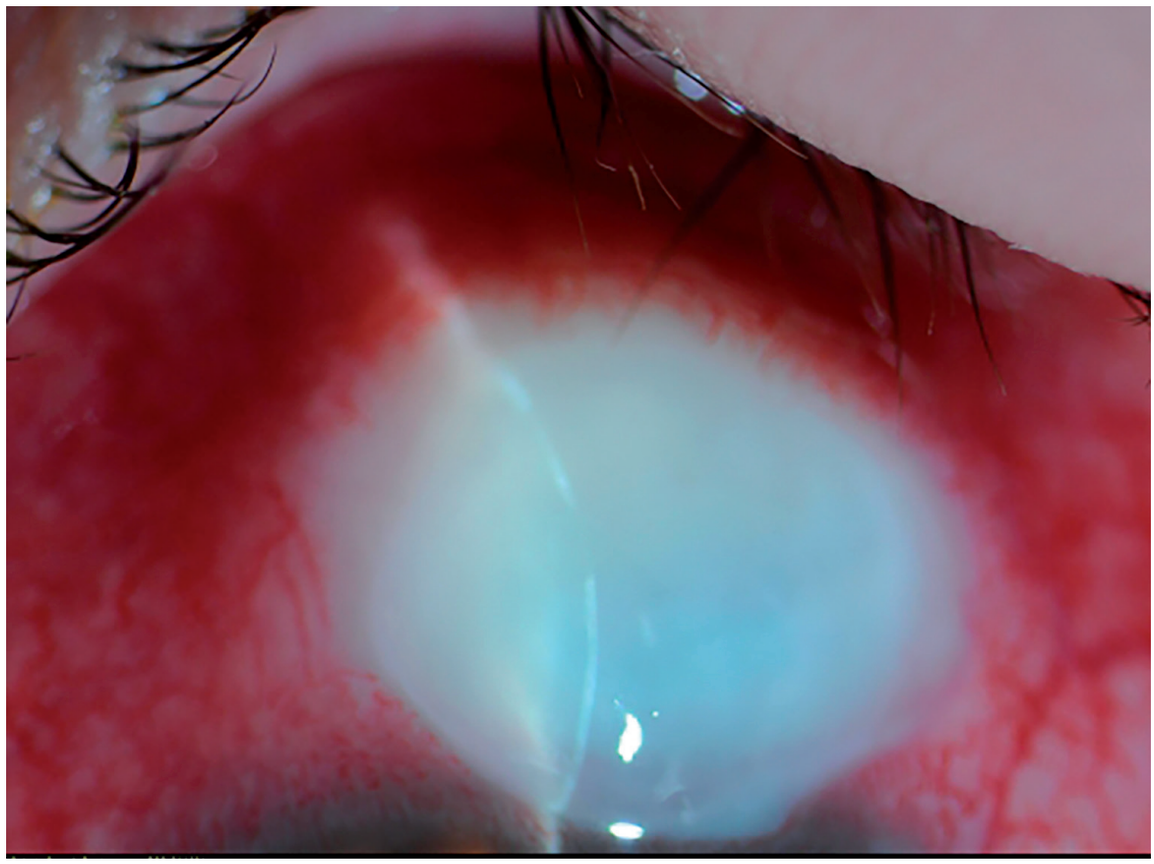

Figure 1.
"White on red" appearance of bleb related infection (notice adjacent blepharitis).

In the author's experience, blebitis can progress to BRE very rapidly, so that if suspected, there must be a low threshold to admit the patient immediately for appropriate targeted treatment (vide infra).

4. Risk factors

Risk factors for BRI can be broadly classified under ocular and systemic conditions.

4.1 Ocular risk factors

- Bleb leak, inferior or nasal bleb, high bleb
- Intraoperative and post-operative MMC/5-FU
- Conjunctivitis
- Blepharitis
- Nasolacrimal duct obstruction
- Lens status
- Trabeculectomy alone compared to combined procedure

4.2 Systemic risk factors

- Upper respiratory tract infection
- Diabetes mellitus
- Age
- Season
- Gender

Blebs located inferiorly are at increased risk of infection since there is greater exposure of the bleb to the tear lake with concentrated bacteria, less protection from the upper lid and more mechanical irritation from greater exposure [18]. The risk of infection in an inferiorly located bleb is x4–x 8 higher in eyes treated with antimetabolites [19].

Fornix-based conjunctival flap trabeculectomies are associated with reduced risk of BRI compared to limbal based conjunctival flap peritomy (hazard ratio 3.39) [20]. In one study, the incidence of late-onset BRI decreased from 5.7% to 1.2% following a change from limbal based to fornix based peritomy [21].

The use of antimetabolite agents, e.g., 5-Fluorouracil (5-FU) and Mitomycin C (MMC) has led to an increase in cases of BRI. The incidence before the use of antimetabolites was 0.2–1.5% [22–24]. This has increased to 2–13.0% in 5-FU treated eyes [25–27] and 1.5%–14% of MMC treated eyes [28–31].

Thin, cystic blebs associated with MMC, and 5-FU use are more prone to infection than blebs with a thick wall [32–35]. They are also associated with late bleb leak (leakage after 4 weeks), another risk factor for BRI [36–38].

In one study, the rate of BRI was 7.9% and 1.7% for blebs with and without leakage, respectively (202). The presence of bleb leak was associated with a 4.7-fold increase in the risk of BRI [38]. Bleb leak must therefore be addressed in an urgent manner by the glaucoma team.

Blepharoconjunctivitis is associated with microbial colonisation of the ocular surface, which is a risk factor for BRI [39–43].

An important practice pearl is to examine the ocular adnexa pre-operatively and to prepare the ocular surface in case of pre-existing blepharoconjunctivitis or nasolacrimal duct obstruction. Furthermore, post-operatively, all patients with an active bleb should be examined for blepharitis.

In patients with a filtering bleb and blepharoconjunctivitis, a short course of topical antibiotic (e.g., fucithalmic, tobramycin, bacitracin, or erythromycin) plus eyelid hygiene is recommended with prompt discontinuation of antibiotic upon resolution. However, the eyelid hygiene must be continued indefinitely. Rosacea blepharitis responds well to topical azithromycin or oral doxycycline [44]. For chronic blepharitis, 0.01% hypochlorous acid, which is a natural product, is an antimicrobial agent that can be used repetitively and long-term without resistance developing [45].

Aphakia and pseudophakia are associated with higher odds of BRI (6.3 v 2.85) [46]. Absence of an intact posterior capsule may enhance microbial penetration into the vitreous cavity [47].

A slightly lower rate of BRI was found in cases of combined trabeculectomy+ cataract surgery (1.4%) compared to trabeculectomy alone (1.5%) at 2.5 years

post-operatively. The lower rate of thin-walled blebs after a combined operation could explain this observation [39].

Diabetes mellitus (DM) is associated with higher positive conjunctival culture rate than in patients without DM. The severity of diabetic retinopathy is correlated to culture positivity (98). In some studies, 18% of cases of BRI had DM [29, 35, 37, 40–42, 48].

Younger age was found to be a risk factor for infection [49, 50], and severe bleb leak was associated with younger adults (<55 years) (99). In some studies, a high rate of BRI was found in children [51] including 8% chance of late onset endophthalmitis [52].

The association with gender is not clearly proven. Seasonal variation in temperature and humidity may influence the conjunctival flora and therefore, the rate of BRI [53].

5. Microbiology of bleb related infection

The most common pathogens in blebitis are Staphylococcus aureus and Staphylococcus epidermidis [47, 54, 55]. The microbes most commonly associated with blebitis are less virulent than those in BRE, are part of normal lid/lacrimal flora, and produce no exotoxins; therefore, with successful treatment, visual prognosis is good. In a retrospective study, visual acuity was at least 20/25 in all successfully treated patients [17].

The microbes most commonly associated with early BRE include Staphylococcus epidermidis. Late onset BRE is associated with greater percentage of Streptococcus species 31%, and Gram-negatives such as Haemophilus influenzae 23%, Enterococcus 7%, Pseudomonas 7%, and fewer Staphylococcus species 7–22% [39, 48, 56].

When initiating antibiotic therapy for BRI, it is important to consider antibiotic resistance, which is particularly high in staphylococci; nearly half being resistant to methicillin with a high probability of concurrent resistance among methicillin resistant Staphylococcus aureus to other commonly used antibiotic classes [57]. In such cases it is useful to know that vancomycin is active against all gram-positive organisms, including all the methicillin-resistant staphylococci [57, 58].

6. Diagnostic investigations

Sampling of the intraocular fluid for Gram stain and culture is recommended before treatment is initiated. However, empiric treatment should begin promptly while the specimen is being analysed. Working closely with the microbiology department is mandatory in managing these cases.

Intraocular fluid samples should be sent for Gram and Giemsa staining, culture, and sensitivity. Gram stain is positive in approximately 45% of endophthalmitis cases [59]. Vitreous sampling has a higher positive culture rate than aqueous humour, with vitrectomy samples being more culture positive than vitreous tap [60].

Polymerase chain reaction (PCR) is useful in culture negative cases. It is effective in detecting fastidious bacteria, provides a result in a few minutes and is more sensitive than cultures [61, 62]. However multiple samples have to be sent for each micro-organism that the clinician suspects. Biome representational in silico karyotyping (BRiSK) is a new technique for detection of any DNA-based life form and can

detect micro-organisms in PCR negative samples [63]. However, its role in BRI is not established.

Although the majority of glaucoma specialists recommend conjunctival sampling, it must be appreciated that conjunctival culture results in BRI do not generally match the culture results from anterior chamber and vitreous humour samples [32, 39, 64]. Care must be taken not to tear the conjunctiva over the bleb area when taking samples.

7. Treatment modalities

The most effective treatment for BRI consists of a combination of fortified aminoglycoside or ceftazidime with vancomycin, i.e., a broad-spectrum antibiotic combination. Moxifloxacin tends to be the most popular fluoroquinolone of choice due to its higher intraocular penetration and activity against gram-negative bacteria, gram-positive cocci, and atypical pathogens [65–67]. Topical aminoglycosides may be efficacious in BRI caused by fluoroquinolone-resistant Staphylococcus species [68].

Pre-operative 5% povidone iodine instillation in the conjunctival sac is recommended in the prophylaxis of endophthalmitis for cataract surgery, and the author recommends the same for glaucoma drainage surgery. It has also been used in the treatment regimen for BRI. Povidone iodine is an antiseptic agent which is clinically effective against a broad range of bacteria and fungi. In a British survey, 28% of glaucoma surgeons used povidone iodine in the conjunctival sac to treat BRI [64]. Just one drop of 5% povidone iodine acts rapidly within 2 minutes to reduce the positive swab rate of the ocular surface from 75% to 28% in eyes without active infection [69].

For BRE, a broad-spectrum combination of intravitreal antibiotics that cover gram-positive and gram-negative bacteria can be started empirically before culture results are available [70], e.g., vancomycin and ceftazidime. The author recommends amikacin instead of ceftazidime for beta lactam sensitive patients with cephalosporin cross reactivity.

Practice point: before performing vitreous tap and intravitreal injections in BRI cases, a retinal examination must be performed to exclude retinal detachment or choroidal detachment (which can be associated with bleb leaks and hypotony). If the view is not clear, ultrasound biomicroscopy must be performed to exclude the same.

Vitreous sampling and intravitreal injection in the presence of choroidal detachment could lead to catastrophic choroidal haemorrhage.

The short duration of action of intravitreal antibiotics does limit their efficacy, but generally If there is no improvement after 36–48 h, another intravitreal antibiotic injection can be given in line with culture and sensitivity results, or pars plana vitrectomy (PPV) can be performed [71]. The author's advice is to have a low threshold for PPV in BRE since the infecting organisms tend to be more virulent and the disease course more fulminant than in post-cataract surgery endophthalmitis.

Other modes of administration of antibiotics include the subconjunctival and oral routes. However, subconjunctival antibiotics do not achieve therapeutic levels in the vitreous [72]. A combination of topical and oral antibiotics achieves higher levels in the vitreous than topical therapy alone, but there is no consensus on the use of oral therapy.

Although, antibiotics are the mainstay of treatment for BRI, consideration should also be given to treating concurrent intraocular inflammation. Therefore, topical cycloplegics should be used to prevent and release posterior synechiae. Topical

steroids should be considered once it is confirmed that the antibiotic treatment is being administered according to sensitivities of cultured organisms and that the treatment is working.

In one study, most of the glaucoma surgeons started topical corticosteroids 24–72 h after the initiation of topical antibiotics [64]. The role of intravitreal steroid therapy lacks evidence but can be considered depending on the response to antimicrobials and the amount of ocular inflammation. Subconjunctival dexamethasone is a reasonable alternative to intravitreal corticosteroids. Steroids are effective in treating inflammation associated with bacterial exotoxins [73] but are contraindicated in fungal disease.

For fungal infections, e.g., severe candida endophthalmitis, a combination of oral amphotericin-B and flucytosine is advised. Fluconazole and oral voriconazole are alternatives that cover a range of fungal species [74, 75]. Usually, a period of 4–6 weeks of treatment is required.

The role of vitrectomy in the setting of endophthalmitis after glaucoma surgery is a matter of debate. The Endophthalmitis Vitrectomy Study (EVS) [60] did not include BRI cases, therefore, strictly speaking, its recommendations cannot be extrapolated to this population. Typically, BRE for example occurs a lot later than the acute setting of post-cataract surgery endophthalmitis. Furthermore, the more virulent organisms found in BRE, would warrant earlier consideration of vitrectomy compared to patients with endophthalmitis following cataract surgery, but evidence-based data to drive this clinical decision are lacking [48, 56]. In cases of fungal BRE, PPV can be sight saving in severe cases [76]. Intravitreal antifungal agents are commonly used in cases of fungal BRE, but evidence for their value is lacking [75]. Intravitreal amphotericin B, voriconazole, and caspofungin are examples of antifungal agents used in BRE [77].

8. Treatment protocol

There is no universally agreed upon regimen, however, the following is the author's preferred practice with reference to what has been discussed in this chapter:

General considerations:

- For all cases of BRI- blebitis and BRE- admit the patient for frequent topical antibiotic therapy and close observation and examination.

- Take ocular samples for culture and sensitivity straight away but start empirical treatment whilst awaiting culture results.

- Blebitis can convert to BRE very quickly, so have a low threshold for pursuing a more aggressive treatment approach if no improvement in the clinical picture is seen in the first 48–72 h (vide infra).

- Examine the patient twice daily during the acute phase of BRI.

- In cases of BRE, fully inform the patient and relatives that there is a high chance of losing vision despite treatment and a low chance of losing the eye.

Specific details:

- If no vitreal involvement, start aggressive broad-spectrum topical antibiotic treatment. Options include fortified antibiotics such as vancomycin (25–50 mg/mL) and cefazolin (50 mg/mL) or fortified tobramycin (14 mg/mL) alternating q30min for 48 h after a loading dose (every 5 min for three doses); or 4th generation fluoroquinolone with same posology.

- Topical cycloplegics, e.g., g Atropine bd can be started straight away; topical steroid, e.g., Prednisolone 1% or Dexamethasone 0.1% qid can be used 48–72 h after initiation of topical antibiotics.

- Taper fortifides after 48 h to regular strength based on improvement.

- If there is vitreal involvement, perform a vitreous tap following all necessary precautions (vide supra) and inject intravitreal antibiotics, e.g., vancomycin + ceftazidime/ amikacin.

- In the absence of fungal infection, consider adjunctive intravitreal dexamethasone (0.4 mg/0.1 mL) which may modify the inflammatory response and consequent damage to retina and other ocular structures.

- If there is improvement in the clinical picture, start tapering the topical antibiotics (vide supra).

- If there is no improvement, refer to retinal surgeons for urgent vitrectomy + intravitreal antibiotics.

9. Visual outcome

In most cases of Infection arising from gram-negative pathogens and streptococci, there is a worse visual prognosis, with only 45–46% achieving best visual acuity (BVA) ≥20/400. In contrast, 89% of eyes achieve BVA ≥20/400 following Infections associated with coagulase-negative staphylococci [78].

Better visual outcomes after BRE are associated with the following:

shorter interval from onset of symptoms to treatment, better initial visual acuity, clear cornea at presentation, isolation of less virulent organisms, and absence of diabetes mellitus [34, 79].

10. Conclusions

- Bleb related infections are uncommon but can lead to blindness in a short space of time.

- Early diagnosis and treatment are crucial to provide the best chance to save sight.

- Patients must be informed of the signs of infection or impending infection- redness, pain, discharge, reduction of vision- and to report to the emergency department immediately if any of these symptoms are experienced.

- Surgeons must play an active role in clinics to look for blepharitis, epiphora or conjunctivitis in the presence of a bleb, and these conditions explained and treated.

- Blebs must be examined at each clinic visit for leakage by Seidel testing, and leaks managed appropriately to prevent further complications.

- Thin, avascular, or sweating blebs, even if not leaking, must be assessed more frequently and the patient informed (vide supra) of the possibility of infection. In such cases it is reasonable to discuss the option of bleb revision.

- Although no clear guidelines have been developed regarding management of BRE, early aggressive treatment is associated with better visual prognosis.

Conflict of interest

"The author declares no conflict of interest."

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