Glaucoma-filtering bleb infections

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Purpose of review

To present a review of the current literature regarding the management of glaucoma-filtring bleb infections.

Recent findings

With the increased use of intraoperative antifibrotic (*eg*, mitomycin and fluorouracil) as an adjunct to standard trabeculectomy, an increased incidence is seen of late-onset filtering bleb-related infections. These infections range from infections localized to the bleb (blebitis) to endophthalmitis. Risk factors for bleb-related infections include an inferior or nasally located bleb; presence of a high bleb or blepharitis; development of a late-onset bleb leak; use of antifibrotic agents; chronic antibiotic use; and performance of a trabeculectomy alone versus a combined procedure.

Summary

The optimal treatment for bleb-related infections is evolving, but consensus is that a high degree of vigilance and aggressive treatment are key to minimizing the potentially blinding nature of this complication. It is important to note that those glaucoma procedures that provide the lowest intraocular pressure are often those that predispose to bleb-related infections.

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Abbreviations

IOP intraocular pressure

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When maximally tolerated medical therapy or laser trabeculoplasty fails to adequately control intraocular pressure (IOP), glaucoma-filtering procedures (*eg*, trabeculectomy) have become the standard of care. To further improve the success of these procedures, it has now become routine to use intraoperative antifibrotic agents (*eg*, mitomycin and fluorouracil) as an adjunct to standard trabeculectomy [1]. Although these agents have improved the chances of long-term IOP control through the creation of thinner blebs that provide enhanced filtration, they have predisposed to an increased incidence of postoperative complications including late-onset filtering bleb-related infections [2•].

A bleb-related infection is classified as blebitis when a mucopurulent infiltrate is identified within the bleb associated with mild to moderate anterior segment inflammation [3••]. Endophthalmitis, on the other hand, is characterized by hypopyon and cells in the vitreous [3••]. It has been suggested that blebitis represent a continuum of infection involving the tissues in the region of the bleb to early endophthalmitis in some cases [4•].

The incidence of blebitis and endophthalmitis after trabeculectomy is higher than most other intraocular procedures [5]. It has been estimated that the prevalence of acute postoperative endophthalmitis after any type of intraocular surgery is 0.093% [6], whereas the reported incidence of late postoperative bleb-related infections after trabeculectomy ranges from 0.4% to 6.9% in several studies over the past decade [5]. The composite incidence from these studies was 1.5% per year and it is believed that this incidence has been increasing, especially considering the increased use of intraoperative antifibrotic agents. Indeed, after trabeculectomy with mitomycin, it is estimated that blebitis occurs with an incidence of 5.7% per year, whereas the incidence of endophthalmitis ranges between 0.8% to 1.3% per year [2•,7,8•]

Because of this increased incidence of intraocular infection after trabeculectomy, much effort has been undertaken to elucidate those risk factors for glaucoma filtering bleb infections. Among the earliest recognized factors was the location of the filtering bleb, specifically an inferior or nasally located bleb [9], with exposure of the bleb to the bacteria-rich tear film. It is known that the tear film contains bacteria known to harbor organisms capable of causing endophthalmitis [10]. One series re-

ported an incidence rate of endophthalmitis as high as 7.8% per patient year with procedures performed at this location [11]. It is also believed that blebs located inferiorly are afforded less protection by the upper lid and may be more susceptible to mechanical irritation from the lower lid [11].

It has also been suggested that the presence of a high bleb and of blepharitis increases the risk of bleb-related infection [12••]. The high bleb may be more susceptible to penetration by pathogens in the conjunctiva and the presence of blepharitis may impart a greater load of bacteria, thus predisposing to infection [12••].

Perhaps, among the most important risk factors for filtering bleb infections is the presence of late-onset bleb leakage [3••]. Eyes with bleb-related infections were 26 times as likely to have a bleb leak detected at the time of infection than eyes without a bleb-related infection, according to a recent case-control study [3••]. The tear film has been shown to have direct access to the anterior chamber via a leaking filtering bleb and, thus, pathogenic bacteria may bypass the conjunctiva and sclera, which provide the main barriers against entry of infectious organisms into the eye [13]. Although it is known that late-onset bleb leak and filtering bleb infections are related, it is not definitively known which comes first, the bleb leak or the infection. Some have argued that bacterial pathogens create a hole in the conjunctiva, whereas others believe that once a hole is created, pathogenic bacteria in the tear film can then cause infection [12••].

Regardless of this debate, it is known definitively that the use of antifibrotic agents leads to a greater rate of late-onset bleb leaks than trabeculectomy without antifibrotic agents. Trabeculectomies performed with fluorouracil have a higher rate of late-onset bleb leaks [15,16] and those procedures performed with mitomycin have an even higher rate of late-onset bleb leaks than those performed with fluorouracil [17,18]. Histologically, blebs after trabeculectomy with mitomycin have irregularities in the conjunctival epithelium, breaks in the basement membrane, and conjunctival and subconjunctival hypocellularity, each of which can predispose to bleb leaks [19–22]. As stated, a late-onset bleb leak is a significant risk factor for filtering bleb infection and a recent study has definitively shown that mitomycin use is strongly associated with development of bleb infection [12••].

Another surprising risk factor that has been highlighted recently is the increased risk of bleb-related infection with intermittent or chronic use of topical antibiotics beyond the immediate postoperative period [12••]. It could be that antibiotics select for virulent bacteria that cause serious infection, but studies have shown that prophylactic use of antibiotics in this situation does not appear to alter the conjunctival flora [23]. This surprising association has not been proved definitively, but it was strongly associated with an increased likelihood of infection [12••]. In terms of variables occurring at the time of surgery, the performance of a full-thickness rather than a guarded filtration procedure appears to increase the risk of bleb-related infection [14]. On the other hand, it has also been shown that the performance of a combined cataract and trabeculectomy versus trabeculectomy alone was protective against the development of infection [12••]. It seems that blebs in eyes that have had combined surgery are thicker than those having trabeculectomy alone [10], thus, these thicker blebs may be less susceptible to bleb leak or infection.

In the early postoperative period, complications (*eg*, flat anterior chamber, early wound leak, and suprachoroidal hemorrhage) have been associated with the development of late-onset infection [24]. It may be that these complications with the filtration procedure later manifest themselves in a bleb that is more susceptible to late-onset infection. For instance, a flat anterior chamber secondary to overfiltration can lead to the development of a thinner bleb that is more prone to infection [12••].

Numerous other possible risk factors exist for blebitis and bleb-related infection, but their relation is not as strong. These include the use of systemic corticosteroids, juvenile glaucoma, silk conjunctival sutures, nasolacrimal duct obstruction, releasable sutures, pale-colored blebs, contact lens wear, bleb-revision surgery, and the use of epinephrine drops in the operative eye [12••,25,26,27]. Other studies have also found a relatively high proportion of men with bleb-related endophthalmitis or bleb-related infection compared with women [3••,28]. Younger age at the time of surgery and black race have also been shown to be elevated risk factors that approached statistical significance [3••].

The spectrum of causative organisms associated with early-onset bleb-related infections is similar to that of acute-onset endophthalmitis after cataract surgery, where the less virulent, *Staphylococcus epidermidis* is the most common organism cultured [29,30]. With early infections, confined to the filtering bleb, the most commonly cultured organisms can also be consistent with the normal flora [31]. So, a positive bleb culture does not always differentiate infection from colonization. Other studies have also shown that an increased association with *Staphylococcus aureus* with blebitis may exist [32].

In early bleb-associated endophthalmitis, the most common bacteria include the coagulase-negative *Staphylococcus sp.* and *Propionibacterium acnes*, which usually have a favorable prognosis for good visual acuity once the infection resolves [33]. In contrast, late-onset bleb-associated endophthalmitis is usually caused by *Streptococcus sp.*

and gram-negative bacteria such as *Haemophilus influenzae*, which have a poorer prognosis for vision [11,31,33, 34•]. It has also been suggested that patterns of infecting organisms have changed in the last 10 years, with *Staphylococcal* infections becoming more common [35]. It may be that the increased use of antiproliferative agents with surgery has led to more bleb leaks with infection by organisms that do not require transconjunctival migration [35].

In terms of treatment for bleb-related infections, no randomized-controlled clinical trials have been conducted to determine the most favorable antibiotic regimen. This is most likely because the diverse variety of infective organisms associated with these infections and the fact that bleb-related infections represent a spectrum from blebitis to bleb-associated endophthalmitis.

Given the potentially devastating effects of endophthalmitis, most clinicians treat a case of blebitis as a cause of endophthalmitis even before the appearance of hypopyon [4•]. Traditionally, in addition to intraocular antibiotics, fortified topical vancomycin hydrochloride (50 mg/mL) and gentamicin sulfate (15 mg/mL) have been the mainstays of bleb-related endophthalmitis therapy [36]. Those with more severe infection and poorer visual acuity at the time of diagnosis usually have immediate pars plana vitrectomy with injection of intravitreal antibiotics [34•].

For those patients felt to have blebitis only, without evidence of vitreous involvement or hypopyon, intensive treatment with topical antibiotics alone may be appropriate [32]. Therapy should be broad-spectrum against the pathogens associated with blebitis until culture results become available.

Considerable controversy exists regarding the use of concomitant topical or intravitreal corticosteroids in the management of late-onset bleb related infections. It is believed that these agents modify the inflammatory response and the resultant damage to ocular structures; however, no research has yet supported their use in this setting [4•]. It has been shown that the use of intravitreal corticosteroids in the treatment of postoperative endophthalmitis reduces the likelihood of obtaining a three-line improvement in visual acuity versus not using corticosteroids [37]. It is not known whether this observation is similar in bleb-related endophthalmitis.

In addition to the role of antibiotic therapy for bleb-related infections, the treatment of filtering bleb leaks may be important [3••]. Numerous 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 [38,39]. However, it may be that patients with late bleb leaks managed with conjunctival advancement have better outcomes and are less likely to have serious intraocular infections versus conservative treatment [40•].

It is important to note that eyes successfully treated for bleb-related infection remain at risk for recurrent infection, which is defined as at least two episodes of bleb purulence with or without associated intraocular inflammation separated by a quiescent period of at least 3 months [41]. Cultured pathogens in recurrent infections are also diverse and no apparent correlation is seen between organisms responsible for the first versus recurrent infections [41]. Interestingly, long-term antibiotic prophylaxis after the first infection did not protect against the development of recurrent infection [41]. Treatment of recurrent infections, with early, aggressive antimicrobial therapy, often permits retention of visual function and successful filtration in recurrent infections [41]. However, the optimal management of blebs with recurrent bouts of infection remains unclear.

In light of the devastating consequences of bleb-associated endophthalmitis, it is critically important to educate patients about the possible lifelong risks, symptoms, and signs of bleb-related infections, which include redness of recent onset, sensitivity to light, visual acuity decline of sudden onset, and pain in the eye [41]. The pneumonic "RSVP" may be helpful to inform patients of these symptoms. By making patients at high risk (those with thin, avascular, or leaking blebs in particular) aware of these symptoms, early diagnosis and aggressive treatment may result in a better visual outcome. Also, clinicians need to be aware that the most successful filtration procedures, in eyes with low IOP and receiving no medications, are at greatest risk for bleb-related infection [12••].

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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