Update on treatment strategies for bleb-associated endophthalmitis

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Purpose of review

Visual preservation in the setting of bleb-associated endophthalmitis has been difficult with existing management strategies. In this article, established findings are compared and potential new treatments that may improve visual outcomes in bleb-associated endophthalmitis are evaluated.

Recent findings

Recent reports have contributed to the existing database of results from bleb-associated endophthalmitis. New systemic antibiotics and novel surgical techniques are also described.

Summary

More options are now available to treat bleb-associated endophthalmitis. No one treatment paradigm is definitively superior in producing desired visual outcomes.

Keywords

bleb-associated endophthalmitis, gatifloxacin, moxifloxacin, 25-gauge vitrectomy, vitrectomy with intravitreal antibiotics, vitreous tap and injection of intravitreal antibiotics

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Abbreviations

BAE	bleb-associated endophthalmitis
EVS	Endophthalmitis Vitrectomy Study Group
MIC	minimum inhibitory concentration
PPV	vitrectomy with injection of antibiotics
tap/inject	intravitreal injection of antibiotics

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Introduction

Endophthalmitis in glaucoma patients with a filtering bleb has been long recognized as a visually devastating disease. Improved glaucoma surgical techniques coupled with better patient access to eye surgeons and facilities have led to an increased prevalence of bleb-associated endophthalmitis (BAE). The incidence of BAE is also increasing due to another factor; widespread use of antifibrotic agents [1]. The ability of glaucoma surgeons to produce a more effective, avascular filtering bleb theoretically leads to easier access of pathologic bacteria into the intraocular space.

An effective management paradigm for patients with BAE has remained elusive. Like many ophthalmic and medical disease entities, the relative scarcity of BAE precludes the use of a level I (prospectively controlled, randomized trial) study to determine the ideal treatment regimen. Current opinions on optimal treatment for BAE rest on the data collected primarily from retrospective case series. Although this level III evidence based data is a useful guide for treatment, it does not allow for a unified statement on the best treatment for these patients.

In this article, the recent peer reviewed publications and presentations relating to the most effective treatment for BAE will be reviewed. Several of these reports do have conflicting treatment outcomes. This is an indication of both the lack of level I evidence based data, and the severity of visual loss in patients who suffer from BAE. Collectively, these reports do contribute to the growing knowledge base that will hopefully benefit patients with bleb-associated endophthalmitis.

Influence of the Endophthalmitis Vitrectomy Study Group

In general, two distinct treatment modalities are employed for patients with endophthalmitis: vitrectomy with injection of antibiotics (PPV), or vitreous tap followed by intravitreal injection of antibiotics (tap/inject). These same two treatment modalities have been reported for patients with BAE [2••,3•,4•,5]. The common theme for both of these treatments is prompt treatment with intraocular antibiotics.

The Endophthalmitis Vitrectomy Study Group (EVS) produced level I results for treatment of a distinct clinical entity, postcataract endophthalmitis. This study demonstrated the efficacy of tap/inject for certain patients with endophthalmitis. Moreover, it demonstrated no benefit from intravenous

ceftazidime and amikacin [6]. It is accepted this postcataract population of patients is distinct from patients with BAE. Numerous reports have demonstrated patients with BAE typically have a delayed presentation of endophthalmitis with more virulent organisms (i.e. predominantly Streptococcal species and also a larger proportion of Gram-negative organisms) [2,5,7•,8••,9,10]. However, a recent study has demonstrated a trend towards treatment of patients with BAE in a similar paradigm to patients with acute, postcataract endophthalmitis [2].

Busbee *et al*. performed a retrospective case series of patients who were treated for BAE in two distinct time periods: the pre EVS years of 1989–1995, and the post EVS years of 1996–2001. The results from these 68 patients did find a potential change in treatment patterns for BAE following the publication of the EVS. There was a significantly higher percentage of patients treated with tap and inject in the post EVS years compared with the pre EVS years (51% vs. 14%, respectively). Additionally, this study noted a significant drop in the use of adjuvant, systemic antibiotics in the post EVS years (Table 1) [2]. The significance of these trends on visual outcomes has not been conclusively determined.

Which is more effective: vitrectomy or tap/inject?

This question remains unanswered. The two largest retrospective case series for BAE have been published in the peer reviewed literature over the past few years [2••,5]. These studies consisted of geographically distinct patient populations with BAE. Interestingly, the evaluation of treatment modalities (either PPV or tap/inject) revealed divergent outcomes in respect to treatment employed.

Song *et al*. reported on 49 patients with BAE. This study demonstrated that approximately one-half of all patients treated with either modality had a final visual outcome of <5/200. Fewer patients treated with PPV in this study achieved vision >20/400 when compared with the tap/inject group (36% vs. 69%). The apparent efficacy of tap/inject was tempered by the authors due to a presumed selection bias. Patients who initially underwent PPV generally had a worse clinical appearance and initial visual acuity. Therefore, PPV was reserved for BAE patients with a more severe infection [5]. Notably, all patients in this study were treated in the post EVS years. An additional confounding variable in these results was that over one-third of patients who initially had tap/inject would also have a subsequent PPV. These patients fell into the cohort of tap/inject for analysis, which could have potentially inflated the efficacy of the tap/inject treatment.

Busbee *et al*. published a similarly designed study of 68 patients with BAE [2••]. Only one-third of patients in this study had a visual acuity of >20/400 at an interval, 12-month posttreatment visual acuity measurement. Unlike the previously described series, this cohort of patients appeared to benefit from prompt PPV compared with tap/inject. The PPV group had a significantly greater likelihood of attaining 20/100 vision. There was also significantly lower rate of no light perception (NLP) vision at 12 months posttreatment in the PPV group (22% vs. 60%, respectively). Subgroup analysis of the most common infecting bacteria, Streptococcal species, also revealed a significantly lower rate of NLP vision with PPV compared with tap/inject ($P = 0.05$) [2••]. It appeared in this patient population of BAE that PPV was superior to tap/inject.

Although these studies yielded opposite primary outcomes [2••,5], there is commonality between these two reports. The most obvious similarity was that a large percentage of patients had poor visual outcomes. Conversely, a minority of patients achieved a posttreatment vision that would be useful for reading or other activities of daily living (Table 2). It is evident that neither PPV nor tap/inject ensure a desired visual result. These reports have also reconfirmed BAE as a more visually impacting disease than its counterpart, postcataract endophthalmitis.

Use of 25-gauge vitrectomy in bleb-associated endophthalmitis

In patients where PPV is determined to be the most advantageous approach to BAE, vitrectomy technique is now a factor to consider for optimal posttreatment outcome. A recent presentation reported on the benefits of 25-gauge vitrectomy compared with traditional 20-gauge vitrectomy in patients with prior glaucoma filtering procedures [11••]. This noncomparative, retrospective series of nine patients demonstrated a superior technique for preservation of

Table 1. Comparison of pre- and post-Endophthalmitis Vitrectomy Study Group pretreatment practices

	Total ($N = 68$)	1989–1995 ($N = 29$)	1996–2001 ($N = 39$)	
Primary therapy				
Pars plana vitrectomy with intravitreal injection of antibiotics	43 (63%)	25 (86%)	18 (46%)	P = 0.002
Vitreous tap alone with intravitreal injection of antibiotics	24 (35%)	4 (14%)	20 (51%)	
Systemic antibiotics				
Used	44 (65%)	28 (97%)	16 (41%)	P ≤ 0.0001
Not used	24 (35%)	1 (3%)	23 (59%)	

Adapted from [2••].

Table 2. Comparison of the two largest bleb-associated endophthalmitis studies

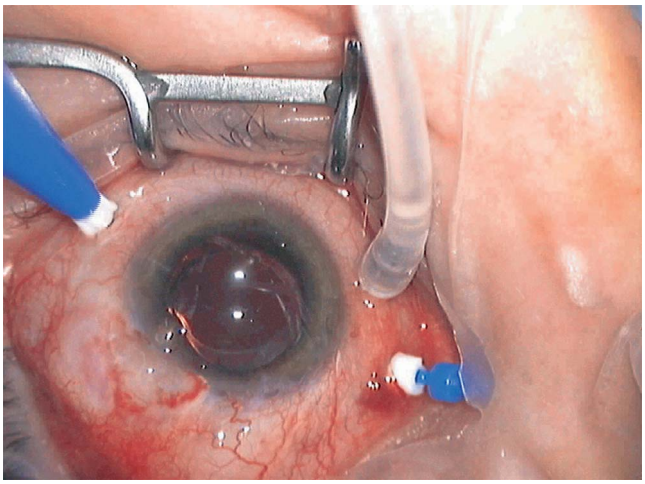
	Busbee *et al.* [2••]	Song *et al.* [5]
Number of patients in cohort	68	49
Mean interval from filtering surgery to BAE	19.1 months	60 months
Primary Therapy		
Pars plana vitrectomy with intravitreal injection of antibiotics	43 (63%)	22 (46%)
Vitreous tap alone with intravitreal injection of antibiotics	24 (35%)	26 (54%)
Visual outcomes		
Percentage of patients with final VA > 20/40	13%	10%
Percentage of patients with final VA > 20/400	34%	53%
Percentage of patients with final VA—no light perception	35%	22%
Visual outcomes for PPV		
Percentage of patients with final VA > 20/40	30% (1996–2001 only)	5%
Percentage of patients with final VA > 20/100	33%	NA
Percentage of patients with final VA > 20/400 or count fingers	56%	36%
Percentage of patients with final VA—no light perception	22%	NA
Visual outcomes for tap/inject		
Percentage of patients with final VA > 20/40	0% (1996–2001 only)	15%
Percentage of patients with final VA > 20/100	13%	NA
Percentage of patients with final VA > 20/400 or count fingers	40%	69%
Percentage of patients with final VA—no light perception	60%	NA

a glaucoma filtering bleb following vitrectomy surgery. Three patients in this study underwent 25-gauge vitrectomy for BAE. In all patients, there was no significant increase in intraocular pressure or need for additional glaucoma medications at 12 months post surgery. All filtering blebs remained functional throughout the study period. This series demonstrated minimal damage to the conjunctiva produced when using the 25-gauge trochar-cannula system. The commercially available 25-gauge system allows for vitrectomy without sutures. This limits the conjunctival inflammation that can lead to bleb scarring and eventual collapse. Figure 1 depicts an intraoperative vitrectomy procedure using the 25-gauge trocar-cannula system. The 25-gauge cannulas were inserted in a position to avoid the superior filtering bleb (Fig. 1). A postoperative photo (day 1) of a patient with a superotemporal filtering bleb is depicted in Figure 2.

This is in contrast to the 40% bleb-failure rate of patients undergoing 20-gauge PPV for BAE noted by Song *et al.* [5]. The high rate of bleb failure in this study is difficult to compare to the small series of 25-gauge vitrectomy patients with filtering blebs. Although the three patients with BAE in Busbee *et al.* did not experience bleb failure after 25-gauge vitrectomy [11••], some failures with a larger cohort would be expected due to the associated inflammation with BAE.

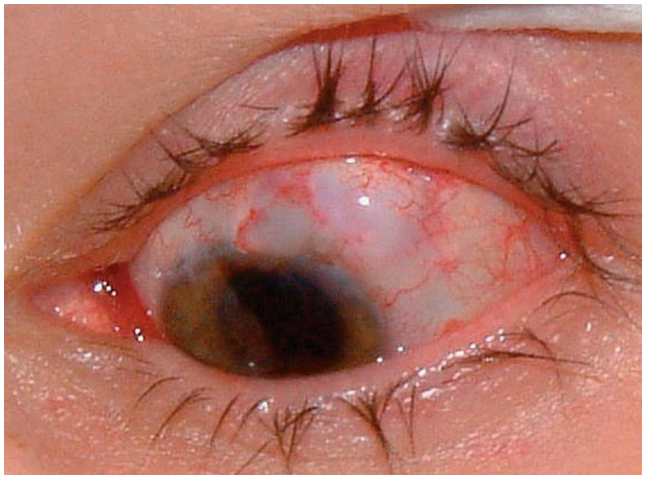
For patients who regain vision following BAE, the preservation of their filtering bleb is critical for preventing

Figure 1. An intraoperative vitrectomy procedure using the 25-gauge trocar-cannula system



The 25-gauge cannulas were inserted in a position to avoid the superotemporal filtering bleb.

Figure 2. A postoperative photo (day 1) of a patient with a supertemporal filtering bleb



There is minimal conjunctival damage present in the immediate postoperative period. The filtering bleb appears to be functional.

further glaucomatous damage. Vitrectomy using a 25-gauge system and instrumentation appears to be a favorable technique when vitrectomy is employed for BAE.

Use of systemic antibiotics: an issue revisited

The role of adjuvant, systemic antibiotics in BAE has not been defined. Once used more frequently in BAE, its use appears to have declined in response to the findings of the EVS [2••]. Since intravenous antibiotics had been demonstrated to be ineffective in the EVS, costly inpatient hospital stays and potential nosocomial comorbidity has been avoided. Until recently, the minimal bioavailability of oral antibiotics in the vitreous cavity did not make it a viable additional treatment. The development of a new generation of antibiotics that more readily cross the blood–eye barrier has led to a renewed interest in systemic antibiotics for endophthalmitis [12]. Recent in vitro and in vivo studies may support the use of oral antibiotics in BAE [13,14].

Mather *et al*. has studied the in vitro susceptibility of 93 bacterial isolates to the fourth generation fluoroquinolones, gatifloxacin and moxifloxacin [13]. This study evaluated the minimum inhibitory concentrations (MIC) for the new, fourth generation antibiotics compared with the third generation fluoroquinolones (ciprofloxacin, ofloxacin, and levofloxacin). The study demonstrated a higher potency with moxifloxacin and gatifloxacin for Gram-positive bacteria. Moreover, these new antibiotics were equally efficacious against Gram-negative bacteria. Another notable finding was the apparent efficacy of moxifloxacin and gatifloxacin against staphylococcal species resistant to the second and third generation fluoroquinolones. This study appears to support another effective antibiotic class against the most commonly affecting BAE organisms, streptococcal and staphylococcal species.

A new, more potent antibiotic must also reach its target site in sufficient concentrations. This has now been demonstrated for gatifloxacin in a well-designed in vivo study by Hariprasad *et al*. [14]. Patients undergoing scheduled pars plana vitrectomy were given an oral loading dose of gatifloxacin prior to surgery. The patients took two doses (400 mg per dose) of the oral antibiotic 12 h apart. Aqueous and vitreous collection times occurred between 3–4 h after the second gatifloxacin dose. Drug concentrations in the aqueous and vitreous were found to exceed the MIC for most of the common pathogens for BAE. Notable exceptions of not achieving an effective intravitreal dose were demonstrated for *Enterococcus* and *Pseudomonas*. This finding is important due to an incidence of approximately 10% of *Enterococcus* or *Pseudomonas* as the infection organism in BAE [2••].

The recent studies demonstrating the efficacy of the fourth generation fluoroquinolones may lead to an increase in its clinical use as an adjunct treatment for BAE. Even with a relatively rapid accumulation of this antibiotic in the vitreous cavity, it will not supplant prompt injection (either by injection or PPV) of antibiotics as the first line therapy. However, oral gatifloxacin may be a relatively cost effective alternative to adjuvant antibiotic therapy. The sustained concentration of a fourth generation fluoroquinolones in the vitreous cavity may be beneficial against the more virulent organisms associated with BAE. This may impart an improved visual outcome. Future studies will need to be performed to give a definitive recommendation regarding the use of an adjuvant oral antibiotic in BAE.

Conclusion

Successful management of bleb-associated endophthalmitis with visual improvement or preservation remains elusive. This is accentuated by the unacceptably high rate of ultimate NLP vision found in the case series evaluating treatments for BAE [2••,5]. The significant morbidity associated with BAE lies within the character of the disease. The presentation is typically insidious and delayed. Moreover, the pathologic bacteria responsible are generally more virulent than other types of endophthalmitis. This confluence of these factors has made the visual outcomes for the patients suffering from BAE quite poor.

The compilation of patients over time may provide better strategies for treating this entity. Currently, some traditional techniques combined with several new advancements may lead to a better clinical outcome. The foundation of a potential good outcome following BAE resides in its prompt initial identification. For the ophthalmologist following patients with glaucoma filtering blebs, a high index of suspicion should be employed for any glaucoma patient with new ocular symptoms. An extended time period from filtering surgery to BAE is the rule, not the exception. Additionally, many of these patients have preexisting visual problems secondary to glaucoma. This makes the evaluation of symptoms more difficult. It has been demonstrated that many patients with BAE will have symptoms as mild as increased irritation and redness. Without proper education of a glaucoma patient to subtle ocular changes, the patient quite often will delay prompt diagnosis by neglecting to contact their ophthalmologist [2••]. This can lead to more severe intraocular damage prior to treatment.

Once BAE is identified, a treatment algorithm should be individualized to the clinical setting and the patient. The merits of PPV vs. tap/inject have not been resolved. Theoretic advantages for tap/inject include the immediate introduction of intravitreal antibiotics. This potentially can eliminate a delay going to the operating room for a PPV. Conversely, PPV intuitively decreases the bacterial load within the infected eye. Considering that more virulent bacteria typically cause BAE, decreasing the bacterial load through vitrectomy may help in preserving retinal function. If a vitrectomy is chosen as the treatment modality,

a 25-gauge vitrectomy system should be employed if possible. This is only applicable if the instrumentation is available and the surgeon has extensive experience using the 25-gauge vitrectomy instrumentation. The 25-gauge vitrectomy technique has been demonstrated to preserve conjunctiva and filtering blebs in patients with BAE [11••]. The advantage of maintaining bleb function and preventing postoperative, intraocular pressure rise in these glaucoma patients is self-evident. The preservation of optic nerve function is essential if a good visual result from treating BAE is to be achieved.

Additional treatment with a course of oral antibiotic is also a new consideration. The studies relating to the fourth generation fluoroquinolones are promising [13,14], although they were not targeted specifically for patients with BAE. Due to the relative infrequent occurrence of BAE, it will take time to critically evaluate these new antibiotics in the setting of BAE. However, empiric treatment with oral gatifloxacin that has theoretic advantages may positively alter the outcome for patients with BAE.

Ophthalmologists treating patients with bleb-associated endophthalmitis must continually reevaluate treatment options and report findings to the ophthalmic community. Through these efforts, a new paradigm using established techniques and novel ideas may lead to improved success in restoring useful vision in patients who suffer from bleb-associated endophthalmitis.

References and recommended reading

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

- • of special interest
- •• of outstanding interest

1 Parrish R, Minckler D. 'Late endophthalmitis'—filtering surgery time bomb? Ophthalmology 1996; 103:1167–1168.

2 •• Busbee BG, Recchia FM, Kaiser R, *et al*. Bleb-associated endophthalmitis: clinical characteristics and visual outcomes. Ophthalmology 2004; 111: 1495–1503; discussion 503.
This large, retrospective study evaluates the efficacy of vitrectomy vs. tap/inject for BAE. Characteristics and infecting organisms are also reported.

3 • Miller JJ, Scott IU, Flynn HW Jr, *et al*. Endophthalmitis caused by Streptococcus pneumoniae. Am J Ophthalmol 2004; 138:231–236.
This is a retrospective series includes patients who had BAE caused by *Streptococcus pneumoniae*.

4 • Yoder DM, Scott IU, Flynn HW Jr, Miller D. Endophthalmitis caused by Haemophilus influenzae. Ophthalmology 2004; 111:2023–2026.
Another retrospective series that includes BAE patients with culture-proven Haemophilus influenzae.

5 Song A, Scott IU, Flynn HW Jr, Budenz DL. Delayed-onset bleb-associated endophthalmitis: clinical features and visual acuity outcomes. Ophthalmology 2002; 109:985–991.

6 Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Endophthalmitis Vitrectomy Study Group. Arch Ophthalmol 1995; 113:1479–1496.

7 • Benz MS, Scott IU, Flynn HW Jr, *et al*. Endophthalmitis isolates and antibiotic sensitivities: a 6-year review of culture-proven cases. Am J Ophthalmol 2004; 137:38–42.
Clinical characteristics of several types of endophthalmitis, including BAE, are described.

8 •• Busbee BG. Advances in knowledge and treatment: an update on endophthalmitis. Curr Opin Ophthalmol 2004; 15:232–237.
A review of several distinct types of endophthalmitis, including BAE.

9 Mandelbaum S, Forster RK, Gelender H, Culbertson W. Late onset endophthalmitis associated with filtering blebs. Ophthalmology 1985; 92:964–972.

10 Kangas TA, Greenfield DS, Flynn HW Jr, *et al*. Delayed-onset endophthalmitis associated with conjunctival filtering blebs. Ophthalmology 1997; 104:746–752.

11 •• Busbee BG Awh CC. Heier JS. Transconjunctival, sutureless 25-gauge vitrectomy: an effective technique for glaucoma patients. American Society of Retina Specialists. San Diego, CA, 2004.
Abstract and presentation of glaucoma patients with filtering blebs who underwent 25-gauge vitrectomy. Conjunctival and bleb preservation was demonstrated in all patients.

12 Durand ML. The post-endophthalmitis vitrectomy study era. Arch Ophthalmol 2002; 120:233–234.

13 Mather R, Karenchak LM, Romanowski EG, Kowalski RP. Fourth generation fluoroquinolones: new weapons in the arsenal of ophthalmic antibiotics. Am J Ophthalmol 2002; 133:463–466.

14 Hariprasad SM, Mieler WF, Holz ER. Vitreous and aqueous penetration of orally administered gatifloxacin in humans. Arch Ophthalmol 2003; 121:345–350.