Idiopathic Vitritis: An Elusive Complication of Boston Keratoprosthesis Surgery

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FOREWORD

This thesis represents the compilation of a year’s work, and a unique opportunity to truly integrate research with clinical management. I immersed myself in this project and truly enjoyed dedicating my efforts to this endeavor.

Over the course of my research year, supported by the National Research to Prevent Blindness Medical Student Eye Research Fellowship, I completed a retrospective review of several hundred keratoprosthesis recipients, and developed a prospective cohort study of affected patients. I enjoyed the opportunity to develop an IRB protocol from the ground up, “Optical Coherence Tomography (OCT) Imaging after Sterile Vitritis,” and ran this research study, overseen by my project advisor. In addition to data analysis, my work involved training in OCT imaging technique and evaluation, and imaging all keratoprosthesis patients presenting to Massachusetts Eye and Ear Infirmary (MEEI) over the course of my fellowship. I also took this opportunity to integrate my research with clinical practice, by participating in keratoprosthesis patients’ clinical visits, as well as actively participating in the management of patients presenting with sterile vitritis throughout their clinical course at MEEI.


Abstracts on topics related to this thesis were presented several times over the course of the research year, each focusing on a different aspect of my research. Two oral presentations were given at the European Society of Cataract and Refractive Surgery Meeting in Ljubljana, Slovenia (“Recurrent Idiopathic Vitreous Inflammation after Boston Keratoprosthesis,” February 2014) and one at the Annual Meeting of the International Ocular Inflammation Society in Valencia, Spain (“Causes of Sterile Vitritis after Boston Keratoprosthesis,” March 2014). I was also selected to give an oral presentation of my work at the Biennial International Boston Keratoprosthesis Conference in Salzburg, Austria in April 2014. I also presented an algorithm for clinical management of post keratoprosthesis vitritis at the Boston Keratoprosthesis Workshop for International Keratoprosthesis Users (“Sterile Vitritis after Keratoprosthesis: Clinical
Management Guidelines,” Massachusetts Eye and Ear Infirmary, Boston, MA, April 2014). This thesis work was featured in the September 2014 Edition of EuroTimes Magazine (“KPro Complication: Recurrent Sterile Vitritis is a Sight Threatening Condition”).

Different aspects of this thesis work were also presented three times at the Massachusetts Eye and Ear Keratoprosthesis Noon Conference, a weekly meeting attended by about fifteen MD and PhD fellows and faculty working on basic and clinical aspects of keratoprosthesis research. I presented a poster at the 2014 Association for Research in Vision and Ophthalmology Annual Meeting (“Sterile Vitritis in the Setting of Boston Keratoprosthesis,” Orlando, FL, May 2014), and was a finalist in the Massachusetts Eye and Ear Annual Meeting poster contest (“Corneal Periprosthetic Tissue Loss in Patients with Idiopathic Vitreous Inflammation after Boston Keratoprosthesis,” Boston, MA, June 2014).

I would like to acknowledge my project advisor James Chodosh MD, MPH, Claes Dohlman MD, PhD, and the research fellows at Massachusetts Eye and Ear Infirmary for their advice throughout my fellowship. I also wish to thank the Research to Prevent Blindness Foundation for their financial support of this work.
GLOSSARY

Boston KPro= Boston Keratoprosthesis
IRB=Institutional Review Board
MEEI= Massachusetts Eye and Ear Infirmary
PMMA=Polymethylmethacrylate
OCT= Optical Coherence Tomography
AS-OCT= Anterior Segment Optical Coherence Tomography
JC= James Chodosh
KAC = Kathryn A. Colby
CHD= Claes H. Dohlman
VA= Visual Acuity
BCVA= Best Corrected Visual Acuity
MOOKP= Modified Osteo-Odonto Keratoprosthesis
MICOF= Moscow Eye Microsurgery Complex in Russia Keratoprosthesis
CMG=Christina M. Grassi
AC=Andrea Cruzat
EVT= Elise V. Taniguchi
BCL=Bandage Contact Lens
ABSTRACT

Introduction: An idiopathic inflammation of the vitreous humor, “sterile vitritis,” has been observed in some keratoprosthesis recipients, typically months to years after implantation. Its etiology is unclear. Potential mechanisms include: 1) local tissue destruction and inflammation around the prosthesis, at the point of contact between cornea donor tissue and the device, 2) microbial cell wall or nucleic acid triggering inflammation, or 3) a systemic immune response with ocular manifestations.

Purpose: 1) To present possible theories for vitreous inflammation, 2) revisit and redefine the clinical paradigm originally attributed to Boston keratoprosthesis recipients presenting with idiopathic culture-negative vitreous inflammation, and 3) investigate one potential mechanism of idiopathic vitritis via a case-control study, using a unique application of anterior-segment OCT imaging.

Subjects: 346 adult patients with a keratoprosthesis, performed by three surgeons (JC, KAC, CHD) at Massachusetts Eye and Ear Infirmary from January 2000 to August 2013.

Methods: A retrospective chart review was performed of the subject group at Massachusetts Eye and Ear Infirmary for demographic data, indication(s) for surgery, timing and presentation of vitreous inflammation, and best-corrected visual acuity at baseline, on presentation, and after resolution of vitritis. Of those in the subject group, 13 KPro eyes with a history of sterile vitritis and 34 KPro eyes without a history of sterile vitritis underwent anterior segment optical coherence tomography (AS-OCT) an average of 3.6 years postoperatively (range 1.9-14.2 yrs). Areas of corneal graft tissue loss (“gaps”) around the KPro stem were identified. Image analysis was performed by two masked observers. The difference in presence, number and size of gaps was compared between cases and controls.

Results: 43 patients were found to have vitreous inflammation between 2 days and 8.5 years postoperatively. 23 cases (43 total episodes) showed no obvious cause for inflammation. 7/23 patients presented with signs and symptoms similar to infectious endophthalmitis but were culture-negative. The number of patients who fit the previous paradigm of sudden painless loss of vision without external signs of infectious endophthalmitis (“sterile vitritis”) was 8 of 23 cases. Vision decline was variable (median loss of 9 lines on Snellen Chart, range 0-24), and median time to recovery of best vision was 8.9 weeks (range 0.86-36.7). 12/23 patients had
repeat bouts of vitritis. 10/43 episodes did not recover to baseline vision. 17/23 patients later developed retroprosthetic membranes (13), glaucoma (8), cystoid macular edema (3), and/or retinal detachment (2). Among sterile vitritis patients imaged using AS-OCT, thirteen patients (13 eyes) had a Type I keratoprosthesis. These patients were compared with 34 Type I controls. There was a significant difference in the proportion of patients presenting with at least 1 gap (11/13= 86%) on AS-OCT as compared to controls (11/34=33.3%, p<0.001). There was a significant difference in the number of gaps between cases and controls (2.6±1.6 vs. 0.5±0.8, p< 0.001), but no significant difference in gap size (0.056 ± 0.049 mm² vs. 0.039 ± 0.025 mm², p= 0.22).

Conclusions: The paradigm for sterile vitritis after keratoprosthesis implantation includes sudden, painless loss of vision with full recovery of vision upon treatment with periocular corticosteroids. However, this existing paradigm does not capture the full spectrum of the disorder. Sterile vitritis after keratoprosthesis can also mimic infectious endophthalmitis, and vision may not recover to baseline despite treatment. A combination of factors likely contribute to each case of idiopathic vitreous inflammation. Specifically, tissue remodeling around the keratoprosthesis may create a dynamic space for inorganic or organic debris to enter the eye. A significantly higher proportion of KPro eyes with sterile vitritis had tissue loss around the KPro stem on AS-OCT than controls. Tissue loss may serve as an entry point for debris or bacterial components, triggering sterile vitritis. Our study underscores the importance of surveillance with AS-OCT imaging in the post-operative management of KPro patients.
INTRODUCTION

Background and State of the Field

Corneal disease is the fourth leading cause of blindness in the world after cataract, glaucoma, and age-related macular degeneration (“Causes of Blindness and Visual Impairment,” World Health Organization). For patients who have failed corneal allograft surgery (corneal transplantation) or are otherwise poor candidates for corneal transplantation, the damaged or diseased cornea can be replaced with an artificial cornea, known as a keratoprosthesis (Aldave 2012, Bradley 2009). The most widely used keratoprosthesis implanted in the United States is the Boston type I keratoprosthesis, developed at the Massachusetts Eye and Ear Infirmary (MEEI), and approved by the Food and Drug Administration for marketing in 1992 (Zerbe 2006). The device has a collar button configuration and is composed of a clear polymethylmethacrylate front plate and stem with a polymethylmethacrylate or titanium back plate (Pearlman 2013, Ueta, In innate Immunity of the Ocular Surface, 2010). A donor cornea sits between the front and back plates with the stem placed through a 3-mm trephined opening in the donor tissue (Figures 1 and 4). Holes in the back plate permit aqueous humor to nourish the donor cornea (Ueta, Ocular Surface Inflammation Mediated by Innate Immunity, 2010).

While the aqueous humor is continuously replenished, the vitreous humor in the posterior chamber is not. The vitreous is a transparent gel, located between the lens of the eye and the retina; the latter lines the back of the eye. The vitreous is avascular, mostly acellular, and composed principally of water. Consequently, if cells or other inflammatory products accumulate in the vitreous, they have a tendency to remain and are slow to clear (Riordan-Eva 2011).

Postoperative inflammation in eyes with a keratoprosthesis remains a problem for some patients and is an area of active investigation. Known complications of keratoprosthesis implantation include retroprosthetic membrane formation, endophthalmitis, and glaucoma (Zerbe 2006, Nouri 2005, Gautam 2012, Lloyd 2001, Nowzari 2008, Gratton 2001, Teronen 1997, see Figure 2). Retroprosthetic membranes represent tissue downgrowth from host corneal stroma, forming behind the keratoprosthesis back plate and thought to develop in response to inflammation (Greiner 2011). Endophthalmitis is an inflammatory condition of the intraocular cavities (ie, the aqueous and/or vitreous humor) usually caused by infection (ibid). Glaucoma, thought to be a
result of surgically induced inflammation and consequent disruption to aqueous outflow, is an ongoing research focus (ibid).

An idiopathic inflammation of the vitreous humor, “sterile vitritis,” has also been observed in some keratoprosthesis recipients, typically months to years after implantation (Zimmerli 2011). This complication has not been rigorously studied before. In the sole publication focused on vitritis in keratoprosthesis recipients, the disorder was characterized as sudden painless loss of vision with vitreous inflammation seen on slit lamp exam, but no other external ocular manifestations (Nouri 2005). At the slit lamp, vitreous inflammation is seen as dust-like particles in the slit beam, suggestive of inflammatory cells (Figure 3). Specifically, patients with idiopathic vitritis were said to lack signs and symptoms of infectious endophthalmitis, such as ocular pain, tenderness, conjunctival injection and edema, and/or ocular discharge, and have negative microbial smears and cultures on vitreous biopsy. In any patient, whether postsurgical or not, where suspicion is high for infectious endophthalmitis on the basis of clinical signs and symptoms, the current standard of care is to rule out infection with a “tap and inject” procedure, in which a small sample of vitreous is taken for smears and culture, followed by intravitreal injection of broad-spectrum antibiotics and sometimes a corticosteroid (typically 1 mg vancomycin, 2.2 mg ceftazidime, 6400 mg dexamethasone). If in a keratoprosthesis recipient, suspicion is low for infectious endophthalmitis (vitreous cells only, without other signs of infection), the paradigm for vitritis put forth by Nouri et al in 2005 recommended that eyes be treated instead with a periocular injection of triamcinolone acetate (20–40 mg) followed by close observation, along with an increase in topical antibiotics in some cases.

In the literature, the term “sterile vitritis” has been ascribed to this complication, given that those patients cultured were negative on vitreous biopsy, and those who were not cultured improved on corticosteroids alone (and therefore presumed to be “sterile,” Nouri 2005). However, this thesis will also refer to the disorder of “sterile vitritis” as “idiopathic vitritis,” given that one of the theories proposed in this work is that “sterile vitritis” may not truly be “sterile.”
Investigation to Date

Sterile vitritis remains the most puzzling complication associated with keratoprosthesis implants, and has not been rigorously studied. It has been addressed in the literature sporadically, and when addressed, has been discussed with considerable uncertainty. Previous work has focused on other complications of KPro, such as the development of retroprosthetic membranes and their histopathology, retinal detachments, and angle closure glaucoma (Robert 2012, Aldave 2009), but no intensive study has ever been focused on sterile vitritis after KPro implantation beyond the case series of Nouri and coworkers.

Importance of the Problem

The Boston KPro has been implanted in only a fraction of patients who would benefit from an artificial cornea, in part because postoperative complications, their avoidance, and optimum management are not yet fully understood.

Given that vision is severely reduced during episodes of sterile vitritis, it is important to understand the pathophysiology behind this serious complication. This severe condition leads to interventions that may or may not be appropriate. For example, the vitreous “tap and inject” procedure can itself be associated with infectious endophthalmitis and retinal detachment. An improved understanding of sterile vitritis is essential toward refinement of the device and its future use in hundreds of thousands of patients who would potentially benefit from an artificial cornea.

Contribution of this Thesis to the Field

This thesis debunks the classical paradigm of sterile vitritis, offering new insight into the clinical presentation of this disorder. This work will present formalized clinical management guidelines for sterile vitritis, an algorithm presented by the author at the Boston Keratoprosthesis Workshop for International Keratoprosthesis Users in April 2014.

In addition, this thesis furthers the use of anterior segment optical coherence tomography (AS-OCT) in providing information about the assimilation of the keratoprosthesis into surrounding corneal tissue. This high resolution cross-sectional imaging modality can help identify those at risk
not only for sterile vitritis but potentially for other complications related to keratoprosthesis placement, such as retroprosthetic membranes, glaucoma, and infectious endophthalmitis.

**Structure of this Thesis**

This thesis has three chapters. Chapter One will revisit the clinical paradigm attributed to idiopathic vitritis, demonstrating that the existing paradigm for idiopathic vitritis does not capture the full spectrum of the disorder. Chapter Two presents potential mechanisms for idiopathic vitritis. Several theories will be proposed in a literature review. In Chapter Three, one of the proposed mechanisms for idiopathic vitritis will be tested in a case-control study, using a unique application of anterior-segment OCT imaging.
CHAPTER ONE: RE-DEFINING THE PARADIGM OF IDIOPATHIC VITRITIS

INTRODUCTION

The purpose of this chapter is to a) re-visit and re-define the clinical paradigm attributed to sterile vitreous inflammation, and b) develop a clinical management approach to patients presenting with features suggestive of idiopathic vitritis, through a large retrospective review of several hundred keratoprosthesis recipients.

METHODS

Institutional Review Board/Ethics Committee approval for this study was obtained from the MEEI’s Human Studies Committee. Patients with vitreous inflammation were identified through a retrospective chart review. Charts were reviewed for all patients who received a keratoprosthesis by 3 surgeons (JC, KAC, and CHD.) between January 2000 and August 2013 at the MEEI, Boston, MA. All patients with any degree of vitreous inflammation after a Boston keratoprosthesis were first identified. For the purpose of the study, vitreous inflammation was defined by the presence of cells and/or vitreous debris on biomicroscopic examination. We chose this inclusive approach to adequately capture the spectrum of presentation of vitreous inflammation in keratoprosthesis recipients (Figure 5). From this larger cohort, patients with no obvious cause for vitreous inflammation served as the focus for the study. The following parameters were recorded from the chart of each patient presenting with vitreous inflammation: age and gender, indication for keratoprosthesis, medical history, ocular history, topical eye medications, presence of glaucoma shunt, polymethylmethacrylate (PMMA) back plate or titanium back plate, events occurring immediately before vitreous inflammation, timing and clinical presentation of vitreous inflammation, results of ocular ultrasound if performed, any adjustments to medical therapy, Gram stain and culture results of intraocular fluid if vitreous tap was performed, time to clearing of the vitreous, timing and presentation of any subsequent episodes of vitreous inflammation, and the best-corrected visual acuity (BCVA) at baseline, on presentation, and after resolution. Baseline vision was that measured at the last appointment before
presentation with vitritis (range of time between baseline vision measurement and vitritis episode was 3 days–3.1 months). Visual acuity (VA) loss was defined as a reduction in the BCVA of greater than or equal to 2 lines on the Snellen chart. All Snellen chart values were converted to logMAR for analysis (Schulze-Bonsel 2006, Holladay 1997). A logMAR change of greater than 0.2 was considered clinically significant.

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 13.0 (SPSS, Inc, Chicago, IL). Normality of continuous variables was tested with the Kolmogorov–Smirnov test. Quantitative variables were expressed as the median and range, and qualitative variables were expressed as frequencies and percentages. The Wilcoxon signed-ranks test was used to compare the progression of BCVA within groups, and the Mann–Whitney test was used to compare between groups. The effect of the treatment method on visual outcome was assessed using a general linear model. All tests were 2-tailed, and statistical significance was considered for p < 0.05.

RESULTS

The median age of patients receiving a keratoprosthesis was 65 years (range, 19–93). Of the patients, 52.5% percent were female. Two hundred seventy-six keratoprostheses were Boston keratoprosthesis type I and 70 were type II (through the surgically closed eyelid, as performed in severe, keratinizing, autoimmune diseases or burns). Of the 346 charts reviewed, 104 patients had an underlying autoimmune disease, and 35 of these had Stevens–Johnson syndrome as the principal etiology of their corneal disease. Forty-three of 346 patients with a keratoprosthesis presented with vitreous inflammation, identified by the presence of cells and/or vitreous debris on biomicroscopic examination. Notably, 5 patients of the 43 were culture positive at diagnostic vitrectomy, consistent with infectious endophthalmitis. Including these 5 patients, a potential triggering event (for example, vitritis in the setting of microbial keratitis, adjacent to the keratoprosthesis) was identified for 20 of 43 keratoprosthesis patients (Figure 5), leaving 23 patients (23 eyes) with idiopathic vitritis (details in Table 1). Patients with a type II keratoprosthesis who developed vitritis within a month preceding an infection (keratitis or
endophthalmitis) were not included in the idiopathic vitritis group because their eyelids may have obscured early clinical signs of infection. Therefore, the proportion of all keratoprosthesis recipients with idiopathic vitreous inflammation was 23/346 patients (6.6%, 1.8 cases per 100 patient-years, see Table 1). Twenty of 23 patients had a type I and 3 had a type II keratoprosthesis. Twelve eyes were aphakic, and 11 eyes were pseudophakic. We found no difference in prevalence of aphakia in keratoprosthesis recipients with idiopathic vitritis as compared with those keratoprosthesis recipients without vitritis (P = 0.51, Fisher exact test). Within the cohort of 23 patients with idiopathic vitreous inflammation, preoperative corneal diagnoses were consistent with the typical range of indications for a Boston keratoprosthesis (Fig. 6, Zerbe 2006, Aldave 2009, Yaghouti 2001). Six of 23 patients had an underlying autoimmune disorder: Stevens–Johnson syndrome (4), idiopathic uveitis (1), and atopy (1). Twenty of 23 patients were on prednisolone acetate 1% at least once daily on initial presentation with vitritis. All patients were using a topical fluoroquinolone at least once daily, and 15 of 23 were using vancomycin (14 mg/mL) once daily. One patient was on polymyxin B/trimethoprim once daily. Nine of 23 patients with idiopathic vitritis had repeat episodes of vitreous inflammation. In total, there were 43 episodes of idiopathic vitreous inflammation. However, the median number of episodes per patient was 1 (see Table 1). All episodes showed vitreous debris on B-scan. The median number of days after keratoprosthesis implantation to the development of the first episode of idiopathic vitritis was 256 (range, 5 days–8.5 years). Symptoms varied widely on presentation (see Table 1). Of 23 patients (43 total episodes), 14 patients (27 episodes) reported a sudden drop in VA. For the remainder, visual loss was described as gradual in onset. Fourteen patients (15 episodes) reported pain on presentation in at least 1 episode. Six patients (6 episodes) presented with symptoms and signs suggestive of infectious endophthalmitis, that is, red painful eye with swelling and discharge (Figure 7). On presentation, 16 of 43 episodes (37.2%) received a vitreous tap for culture and injection of antibiotics and corticosteroids (1 mg vancomycin, 2.2 mg ceftazidime, 400 mg dexamethasone). In 1 episode, coagulase negative Staphylococcus was identified only from meat broth culture. In this particular case, vitreous biopsy was performed in a minor procedure room in the emergency department, and we considered the growth in broth to be a likely contaminant. The remainder of episodes cultured showed no growth on cultures. Seventeen patients (29 episodes) were treated with a retrotenon injection of 20 to 40 mg triamcinolone acetate, and the remainder was treated solely with an increased frequency of topical prednisolone acetate 1%. Both vitreous
“tap and inject” and retrotenon triamcinolone were given in 11 episodes. The median time to resolution of vitreous cells was 65 days (range, 2–300 days). Seventeen patients had sequelae of chronic inflammation on their most recent examination, including retroprosthetic membranes (13), retinal detachment (2), cystoid macular edema (3), and glaucoma (8), with associated decline in the BCVA. Reduction in vision on presentation varied widely, and ranged from no change on the Snellen chart to a decline in 1 patient from a baseline of 20/40 (0.3 logMAR) to light perception (2.7 logMAR) concurrent with the vitritis episode. For the 43 episodes of idiopathic vitreous inflammation (in 23 patients), median VA loss was 9 lines (range, 0–24) on the Snellen chart between baseline vision and presentation with vitritis (Fig. 8). Median VA gain between presentation and best post-episode vision was 8 lines (range, 28 to 22).

Overall, patients had a median VA loss of 1 line between baseline and best post episode vision (range, 28 to 10). However, on average, no vision was lost after vitritis resolution (P = 0.36; Wilcoxon signed-rank test). For the 43 episodes of idiopathic vitreous inflammation (in 23 patients), 28 episodes resulted in return to baseline BCVA within 2 lines on the Snellen chart (Figure 8). Seven episodes resulted in a greater than 2 line BCVA loss from baseline. In 3 episodes of idiopathic vitreous inflammation, the final VA was better than that before onset of vitritis. Five episodes had incomplete data and were excluded from this analysis. Approximately 80% of episodes were followed by full recovery to baseline vision. For those episodes where patients had permanent loss of baseline vision, there was no obvious underlying explanation. The median time to best vision for all episodes was 9.4 weeks (range, 0.3–56). Of those episodes that were treated with retrotenon triamcinolone, the median time to recovery of best vision was 8.6 weeks (range, 1–36.7). Of those episodes that were treated only with topical corticosteroids, the median time to recovery of best vision was 9 weeks (range, 0.3–56). Patients who took longer to recover (greater than 9 weeks) did not have worse visual outcomes. In those receiving triamcinolone, the median change in the BCVA before and after sterile vitritis was 0 (range, 29 to 3). This was also true for patients not receiving triamcinolone (median, 0; range, -9 to 2). There was no statistically significant association between triamcinolone injection and full recovery of BCVA (P greater than 0.5, Fisher exact test, 2-tailed). Both groups (the triamcinolone group and topical corticosteroids-only group) had similar vision before the vitritis episode and after treatment (P greater than 0.92; Mann–Whitney U test). The 2 methods of administration had no effect on the visual outcome (P greater than 0.54; repeated measures within-subject effect). Factors considered as possibly
associated with pathogenesis of idiopathic vitritis after keratoprosthesis implantation included preexisting autoimmune disease and the type of material in the keratoprosthesis back plate. The proportion of patients with autoimmune disease who developed idiopathic vitritis after a keratoprosthesis was 5/104 (4.8%). The association between autoimmune diseases and developing idiopathic vitritis was not statistically significant (P = 0.49, Fisher exact test, 2-tailed). Four of 23 patients with idiopathic vitritis had Stevens–Johnson syndrome. The association between Stevens–Johnson syndrome and idiopathic vitritis was also not statistically significant (P = 1.0, Fisher exact test, 2-tailed). Twelve of 23 patients had a titanium back plate, and 11 of 23 patients had a PMMA back plate. The proportion of patients with titanium back plates who did and did not develop sterile vitritis was 12/120 (10%) and 108/120 (90%), respectively. The proportion of patients with PMMA back plates who did and did not develop sterile vitritis was 11/169 (6.5%) and 158/169 (93.5%), respectively. The association between back plate material and developing vitritis was not statistically significant (P = 0.38, Fisher exact test, 2-tailed).

**DISCUSSION**

Despite advances in the Boston keratoprosthesis design and postoperative care, vitreous inflammation after implantation of this device is a poorly understood complication. Ours is the first in-depth study to examine all causes of vitreous inflammation after a keratoprosthesis. We identified several likely causes related to the onset of vitreous cells in many patients, including immediate postoperative inflammation, response to local trauma, hemorrhage, keratitis, and corneal melt. These causes are known to stimulate an inflammatory response, and all typically respond to corticosteroids and/or topical antibiotics (Greiner 2011, Chan 2012, Utine 2011). However, there were also many cases for which we could not clearly identify a cause; we defined these as idiopathic. In our study, the proportion of patients whose initial onset of keratoprosthesis-related sterile vitritis fit the previous paradigm was only 4/23 (Nouri 2005). Of note, 1 of these 4 patients had additional episodes that did not present in a classical fashion. Therefore, patients with idiopathic (sterile) vitreous inflammation after keratoprosthesis implantation may often present with gradual loss of the BCVA and/or clinical signs that mimic those of infectious endophthalmitis. Signs and symptoms of sterile vitritis fall on a spectrum, rather than fitting neatly into subgroups.
Although the median change between baseline and post-episode BCVA in our study was negligible, full visual recovery is not guaranteed in all patients. Twenty-five percent of patients lost greater than 2 lines of vision from baseline, and 36% reported subjective VA loss that was permanent. Possible reasons why treatment did not always result in full visual recovery include macular edema and/or retinal photoreceptor cell damage (Kang 2012, Nguyen 2011). Surprisingly, 3 patients had better vision after resolution of vitritis than their best vision before vitritis. We speculate that these patients may have had subclinical macular edema before the onset of vitritis, which subsequently improved with administration of corticosteroids. One patient had a tight contact lens replaced with a lens with a flatter base curve on the visit preceding the episode of sterile vitritis; the tight lens may have prevented the patient from achieving best-corrected vision at the pre-vitritis visit. Only 1 patient in our cohort developed idiopathic vitreous inflammation less than 2 months after surgery (5 days postoperatively). We included this patient in our cohort because her eye was initially quiet after surgery, followed by vitreous cells out of proportion to standard postoperative inflammation. Vitreous smears and cultures were negative. Vision loss in our cohort also did not resolve as promptly on corticosteroids as previously described (Nouri 2005). The median time to BCVA was 9.4 weeks (range, 0.3–56 weeks), compared with that previously described (4–9 weeks). Patients with milder presentation were typically treated with increased topical corticosteroids alone. Triamcinolone injection was performed when patients exhibited what the clinician perceived to be a significant degree of vitreous inflammation or in those that did not improve after an increase in the frequency of topical corticosteroids. Patients treated with retrotenon triamcinolone achieved similar vision to those treated with topical corticosteroids, similar time to maximal visual recovery, and similar time to clinical resolution of vitreous cells. However, because these 2 groups likely differed in clinical severity, a statistical comparison of outcomes comparing triamcinolone and topical corticosteroids may not be meaningful. Repeated retrotenon injections of triamcinolone might hasten recovery but could also lead to increased complications. Previous studies have suggested that continuous delivery of relatively low doses of corticosteroids to an eye with sterile vitreous inflammation may be more effective than intermittent bolus delivery of higher doses because corticosteroids have complex dose–response curves (Beer 2003, Campochiaro 2010). Insertion of a triamcinolone intravitreal implant in patients with chronic noninfectious posterior uveitis has been successful and may be a future option for keratoprosthesis recipients with recurrent sterile vitritis (Campochiaro 2010).
Autoimmune diseases are associated with an increased complication rate after keratoprosthesis surgery, including corneal ulceration and infection (Zerbe 2006, Aldave 2009, Bradley 2009, Chew 2009). Keratoprosthesis patients with Stevens–Johnson syndrome more commonly develop keratolysis, glaucoma, and retroprosthetic membranes than patients with nonautoimmune diseases, leading potentially to aqueous leakage, hypotony, and retinal detachment (Sayegh 2008). Our sample size was small, but we did not find an association between autoimmune disease and sterile vitreous inflammation after keratoprosthesis implantation.

We cannot rule out the possibility that some of our patients developed intraocular inflammation due to a viral uveitis. Four of 23 patients had a history of either herpes zoster ophthalmicus or herpes keratitis (see Table 1). One patient with a history of zoster experienced multiple recurrent vitritis. In a keratoprosthesis patient with a history of herpetic infection who develops vitritis, viral reactivation must be considered as a possible cause.

Titanium was previously found to be associated with less retroprosthetic membrane formation than PMMA when used as a material for the keratoprosthesis back plate (Todani 2011). We did not find any statistically significant difference in the incidence of sterile vitritis in those with titanium versus PMMA back plates. The choice of back plate material does not seem to play a role in this phenomenon based on our data. After vitritis, 17 patients developed sequelae of chronic inflammation (retroprosthetic membrane, retinal detachment, cystoid macular edema, glaucoma). This suggests a potential common inflammatory pathway after a keratoprosthesis. Sterile vitritis may be one of the first signs portending these other developments. However, our study was too small to definitively conclude a relationship between sterile vitritis and any of the above sequelae. The etiology of idiopathic vitreous inflammation after keratoprosthesis implantation remains unclear, and there could be more than one cause. Potential mechanisms include one or more of the following: (1) microbial cell wall or nucleic acid triggering noninfectious inflammation, (2) local tissue destruction around the prosthesis, perhaps due to microscopic movement of the prosthesis, triggering expression of inflammatory cytokines, and (3) a systemic immune response with ocular manifestations, such as that in primary uveitis. One patient in our study had preexisting chronic uveitis that may have contributed to vitritis after keratoprosthesis implantation. Twenty of 23 patients were on prednisolone drops when the episode occurred, making it less likely that vitritis was related to corneal allograft rejection. These theories will be discussed further in Chapter Two.
Sterile vitritis has also been observed in other keratoprosthesis devices, such as the modified osteo-odontokeratoprosthesis, in which idiopathic vitritis was seen in 3 of 50 patients in one study, and in another report, the MoscowEye Microsurgery Complex in Russia Keratoprosthesis, in which idiopathic vitritis was seen in 5 of 15 patients (Iyer 2010, Huang 2011, 2012). Signs and symptoms on presentation of sterile vitritis in the setting of other keratoprosthesis designs appear similar to those described above with the Boston keratoprosthesis.

Clinical Management of Sterile Vitritis

A proposed treatment algorithm for clinical management of vitreous inflammation after keratoprosthesis implantation is shown in Figure 9. For keratoprosthesis patients presenting with vitreous inflammation on slit-lamp examination, the clinician should first consider known causes for vitreous cells, most importantly, infectious endophthalmitis, but also immediate postoperative inflammation, hemorrhage, trauma, keratitis, or wound leak. For idiopathic cases in which vision has declined in the setting of vitreous inflammation but in an otherwise quiet eye, the clinician is advised to begin with topical corticosteroids, followed by close observation, recognizing that patients may require one or more retrotenon triamcinolone injections to hasten visual recovery. Typically, noninfectious cases will respond to increased frequency of corticosteroid administration, but even infections can seem to respond in the short term (Clark 1999). Concern should arise for those episodes that do not respond to corticosteroids, or respond initially but then acutely worsen. Also, patients with altered local (ocular) immunity and/or systemic immune suppression may not mount a typical response to an infection (Utine 2011, Streilein 1997). Therefore, the clinician should always be aware of the possibility of infectious endophthalmitis, even in the absence of overt clinical signs (Ray 2002). Devastating reduction in vision and even loss of the eye with a keratoprosthesis can occur if intraocular infection goes untreated (Chan 2012, Ray 2002, Durand 2009, Ramchandran 2012, Robert 2012). During the course of our study, 5 keratoprosthesis patients with vitreous inflammation were found to have infectious endophthalmitis. Three lost vision permanently, and one of these required enucleation. However, patients with vitreous inflammation who have negative cultures and smears after vitreous biopsy with no improvement despite intravitreal antibiotics can usually be treated safely with topical and/or retrotenon corticosteroids.
In this chapter, we have revisited the clinical paradigm attributed to idiopathic vitritis, and demonstrated that this existing paradigm does not capture the full spectrum of the disorder. Our next task is to delve deeper into potential causal mechanisms for idiopathic vitritis, to be discussed in Chapter Two.
CHAPTER TWO: POTENTIAL CAUSES OF IDIOPATHIC VITRITIS AFTER BOSTON KERATOPROSTHESIS SURGERY

In keratoprosthesis recipients who required surgery due to preexisting, severe, ocular surface disease, baseline innate immunity is disrupted, with an unstable ocular surface, altered microbial flora, and chronic ocular inflammation (Pearlman 2013, Ueta 2010).

What causes vitreous inflammation? The etiology is unclear, and there could be more than one explanation. Among the potential mechanisms, i) local tissue destruction and inflammation around the prosthesis, at the point of contact between cornea donor tissue and the device, ii) microbial cell wall or nucleic acid triggering inflammation, and iii) a systemic immune response with ocular manifestations, all seem feasible. This literature review addresses these three theories. First, sterile inflammation in joint and dental prostheses will be reviewed, as this may provide insight into sterile inflammation after keratoprosthesis. Culture-negative vitreous inflammation seen in other keratoprosthesis devices will also be addressed. A combination of the three theories described above may be responsible for sterile vitritis after a Boston keratoprosthesis.

A dental implant shares many similarities with the Boston keratoprosthesis. Both reside in a similar mucosal environment, are composed of nonbiologic, artificial components, and are designed to integrate into the host environment with minimal disruption to surrounding tissues (9, 10). Titanium alloys used in dental implant surfaces stimulate the in-vitro production of inflammatory cytokines, and in particular, IL1- β (Nowzari 2008). Micromotion of the dental implant has also been shown to induce sterile inflammation (Gratton 2001), characterized by chronic leukocyte recruitment and excessive production of matrix metalloproteinases (enzymes involved in wound healing), causing the pathological breakdown of surrounding host tissues (Teronen 1997). Tissue destruction can be an entry point for microbes from the mucosal surface (Zimmerli 2011). Lipopolysaccharide, a cell wall component of gram-negative bacteria, further stimulates cytokines and breakdown of peri-implant tissues (Howes 1994). This leads to a vicious cycle, in which cell death triggers increased expression of inflammatory cytokines and peri-implant damage, and eventual loosening of the implant (Zimmerli 2011).
While knee and hip joint implants reside in a different biologic environment than a keratoprosthesis, both devices use similar biologically inert materials and integrate mechanically with surrounding host tissue (Gautam 2012, Long 1998, Rajpura 2014). However, the integration is not seamless; inflammatory cells cannot opsonize bacteria adequately at the tissue/implant interface, a process previously described as “frustrated phagocytosis” (Zimmerli 2011). This leads to increased bacterial adherence to the device, forming a “biofilm.” These bacteria can remain relatively protected from clearance by the host’s immune system, cause persistent or intermittent low-grade inflammation, and are often resistant to antibiotics (Goodman 2013). Such biofilms are also found in oral implants (Heuer 2007).

Sterile vitritis has also been observed in other keratoprosthesis devices. Sterile vitritis was seen in 3/50 recipients of the modified osteo-odonto keratoprosthesis (MOOKP) in one study (21), and 5/15 cases implanted with the Moscow Eye Microsurgery Complex in Russia Keratoprosthesis (MICOF) in another (Huang 2011). Signs and symptoms on presentation with sterile vitritis were similar to those described above with the Boston keratoprosthesis.

While the MICOF prosthesis is also composed of polymethyl methacrylate and titanium, the MOOKP prosthesis is made from polymethyl methacrylate and dental tissue (Huang 2011). This suggests that sterile vitritis might be a reaction to polymethyl methacrylate. However, intraocular lenses of the same material do not induce vitritis. Therefore, sterile vitritis after keratoprosthesis is likely not a reaction to a specific synthetic material. In our review of 346 patients who received a KPro between 2000 and 2013 at Massachusetts Eye and Ear Infirmary, we did not find any statistically significant difference in the incidence of sterile vitritis in those with titanium versus polymethylmethacrylate back plates (Grassi 2015). The choice of back plate material does not appear to play a role in this phenomenon based on our data.

Similar to a dental implant, our first theory proposes that the interaction between the relatively flexible donor corneal tissue and the rigid prosthesis at the point of contact may stimulate inflammation as a component of tissue remodeling (Figure 4). We know from fundamental mechanisms of immunology that chemokines successfully recruit an influx of inflammatory cells only once threshold levels of chemokine protein have been reached (Pearlman 2013). Recurrent corneal cellular stress adjacent to the keratoprosthesis stem could incite expression of metalloproteinases and proinflammatory cytokines that trigger tissue remodeling and inflammation (Tan 2012). The presence of sharp edges on the keratoprosthesis adjacent to corneal
tissue could contribute to the inflammatory response. Chronic stimulation of proinflammatory mediators at the junction of the donor tissue and keratoprosthesis stem may on occasion exceed the threshold necessary to induce acute inflammation.

Corrosion from titanium alloys has been documented in dental implants, and polymethyl methacrylate is known to release small particles in orthopedic implants (Singh 2007, Green 2013). However, to our knowledge there are no published reports of KPros in situ or those explanted, with evidence of physical degradation.

Our second theory proposes that microbial cell wall or nucleic acid can trigger vitreous inflammation after keratoprosthesis implantation. These could occur through either of three mechanisms. First, clinically inapparent infection or colonization of the corneal carrier of the keratoprosthesis or the prosthetic material, respectively, could cause infectious vitritis that appeared “sterile” if the organism was not culturable by standard methodology. However, in sterile vitritis, microbes are characteristically absent on stained smears taken from the vitreous gel, making this scenario unlikely (Nouri 2005). Second, microbial components such as bacterial cell wall or nucleic acid from nonviable bacteria could enter the eye through a gap between the device and the adjacent corneal tissue, and induce intraocular inflammation manifest as sterile vitritis. For example, endotoxin is a heat-stable lipopolysaccharide component of cell membranes of gram-negative bacteria. Bacterial endotoxin stimulates macrophages via interaction with CD14 and toll-like receptor 4 (Pearlman 2013). Inorganic debris in the tear film could also enter through a gap that forms between the keratoprosthesis and corneal donor tissue, for example, during eye-rubbing or blinking. This mechanism relies on tissue remodeling around the keratoprosthesis, and this in turn may explain why the complication often occurs months to years after implantation. If eye rubbing were in fact a risk factor, encouraging patients to wear an eye shield at night may be an effective clinical strategy to prevent sterile vitritis.

“Biofilms,” as previously discussed, could also be responsible for sterile vitreous inflammation after keratoprosthesis, as described in dental and orthopedic implants (Zimmerli 2011, Goodman 2013, Heuer 2007). All patients with a Boston keratoprosthesis are maintained on chronic topical broad spectrum antibiotics, typically a fluoroquinolone and vancomycin, which keeps bacterial flora suppressed. Daily topical antibiotics have led to a reduction in bacterial endophthalmitis rates to less than 1%, but do not likely prevent biofilm formation (Durand 2009). Such biofilms may also be difficult to culture by standard methods. One might also consider
contamination of the implanted device. The keratoprosthesis is extensively tested for residues and bioburden prior to shipping, and given the delayed onset of vitritis, “spoiling” at the time of surgery or contamination are unlikely.

Third, the threshold of cytokine recruitment may be more easily reached if there is a systemic immune response to another trigger. Two patients in our sterile vitritis case series presented with recurrent episodes after dental work or a short-lived gastrointestinal illness. The eye appears to be highly and selectively sensitive to the pro-inflammatory effects of lipopolysaccharide of gram-negative bacteria (Howes 1994). A low dose of lipopolysaccharide given at a site remote from the eye induces an acute breakdown in the blood-aqueous barrier and the influx of acute inflammatory cells into the anterior uvea and anterior chamber (Howes 1994). Patients could be bacteremic from other causes, generating a systemic immune response and secondary vitreous inflammation.

Rather than a single mechanism, a combination of these three factors likely contributes to each case of idiopathic vitreous inflammation. In particular, tissue remodeling around the keratoprosthesis may create a dynamic space for inorganic or organic debris to enter the eye. Some cases of vitritis may have an infectious origin, despite negative cultures. Given the spectrum of presentation, i.e. ranging from 1-2+ vitreous cells to flocculent vitritis with symptoms mimicking infectious endophthalmitis, the load or quantity of the organism may determine clinical severity in these cases. Components of bacteria, such as cell wall components (lipopolysaccharide, peptidoglycan, lipoteichoic acid and capsular polysaccharide) activate cytokine cascades even if the organisms themselves are inactive or of low virulence (Callegan 1999). In our review of cases, there was no association between patients with auto-immune disease and sterile vitritis (Grassi et. al 2015). This suggests that the etiology is likely mechanical, as described above, and not an auto-immune phenomenon.

Continued studies are needed to assess the clinical significance of corneal tissue loss under the front plate and adjacent to the stem. These areas of tissue “gaps” may provide access for organic and inorganic debris to enter the eye and stimulate inflammation. Prevention of biofilm formation may also be important in preventing sterile vitritis. An implant coating for the Boston keratoprosthesis may need to be considered, i.e. one that will release pre-incorporated bactericidal agents such as antibiotics, antiseptics, silver ions, or growth factors to disrupt the life cycle of colonizing microbes. Certain polymer coatings such as polyethylene oxide or protein resistant
polyethylene glycol can result in inhibition of bacterial adhesion (Kaper 2003, Kingshott 2003). Antibiotics have been incorporated in polymethylmethacrylate bone cement for total joint arthroplasty, and loaded onto titanium joint implants as part of a hydroxyapatite coating (Zimmerli 2011, Goodman 2013). Silver could also be used due to its inhibition of bacterial adhesion, long-lasting effect, and resistance (Goodman 2013).

In summary, the etiology of sterile vitritis in keratoprosthesis recipients remains unknown. The mechanisms proposed above are certainly not the only ones possible, but may be contributory. As the number of keratoprosthesis recipients increases, further work is needed to determine the etiology of sterile vitritis or improved clinical management and prevention. In Chapter Three, one of these proposed mechanisms will be investigated in a case-control study.
CHAPTER THREE: A UNIQUE APPLICATION OF OCT IMAGING: PROBING THE ETIOLOGY OF IDIOPATHIC VITRITIS

INTRODUCTION

This chapter specifically addresses one of the aforementioned hypotheses, that of tissue gaps promoting access to the eye’s interior. A potential space exists between the front plate stem and the corneal donor tissue (known as the keratoprosthesis–donor cornea interface). Epithelium may cover the interface between the cornea donor tissue and the edge of the keratoprosthesis front plate over time. However, this epithelial “seal” does not occur in all patients or at least not in a 360 degree circumference (Sippel 2012). These potential spaces could be entry points for microorganisms or inorganic debris to enter the eye.

Anterior segment optical coherence tomography (AS-OCT) allows non-invasive, non-contact, high-resolution cross-sectional imaging of the anterior segment also of patients with a keratoprosthesis (Kang 2013, Radhakrishnan 2011, Shapiro 2013, Cruzat 2013). It is useful for identifying patients with areas of corneal tissue loss since the device and carrier graft can be visualized, as well as the relationship of the corneal tissue to both the anterior and the posterior surfaces of the KPro front plate and along the stem. This may not be readily seen on slit-lamp exam.

The purpose of this imaging study was to test our hypothesis that sterile vitritis after KPro implantation may be associated with microscopic gaps between the KPro stem and adjacent corneal tissue. Components from killed bacteria may enter the interior of the eye through these gaps. KPro patients with a history of idiopathic sterile vitritis at any point after surgery were compared with controls to determine if an association exists between peri-prosthetic corneal tissue loss and the development of sterile vitritis.
METHODS

Approval from the Human Studies Committee Institutional Review Board (IRB) at the Massachusetts Eye and Ear Infirmary was obtained. This study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and was conducted according to the principles expressed in the Declaration of Helsinki. HIPAA authorization and written consent were obtained from all patients. Exemption and waiver for HIPAA authorization and written consent were granted for the retrospective collection of patients in the control group.

Patients with idiopathic vitreous inflammation were imaged with AS-OCT with RTVue Optovue OCT ® (Fremont, CA). Details of the application of AS-OCT technology in keratoprosthesis eyes have been previously described (Cruzat 2013). Briefly, all subjects underwent anterior segment imaging using spectral domain optical coherence tomography (RTVue, Optovue, Fremont, CA). All images were acquired in standard light conditions without removal of the bandage contact lens, except in one patient with a cosmetic contact lens that required removal prior to imaging. Eyes were scanned in all 4 quadrants (inferior, superior, nasal and temporal) with the low-magnification corneal lens adapter (CAM-L) in raster mode (Figure 10). The raster mode provides 17 images at a 250 micrometer distance between raster images, and we imaged the 4 quadrants around the stem. This allows to obtain images from the 360 degree circumference of the keratoprosthesis-corneal tissue interface. The CAM-L lens provides a scan length of 2 to 6 mm and an image size of 12 x 8 mm.

A “gap” was defined as an area of corneal tissue loss at any point underneath the front plate and abutting the stem. Gaps were identified as hypo-reflective (black) regions of tissue loss found within the hyper-reflective (white) corneal tissue adjacent to the keratoprosthesis stem and under the front plate. The best quality AS-OCT images identifying gaps in both cases and controls were selected and quantified by masked observers using the RTvue measurement tool by circumscribing by hand with the polygon tool. The gap area in square millimeters was recorded (Figure 11A). Areas of noncontiguous corneal tissue loss were considered two separate “gaps” and measured individually. Measurements were performed by two masked observers (CMG and AC), and the average of the two measurements were used in analysis. The difference in the presence of gaps, number of gaps, and size of gaps between control patients and cases was tested using the two-
tailed Student’s t-test for unpaired samples. The Odds Ratio was also calculated to quantify how strongly the presence of corneal tissue gaps was associated with a history of sterile vitritis.

The position of gaps was classified (front-plate, stem, or combined gap) depending on location under the front plate or adjacent to the stem. Gaps located both under the front plate and along the stem were classified as “combined” gaps (Figure 11). The presence of epithelial tissue extending over the anterior surface of the keratoprosthesis front plate was also noted and defined as an “epithelial lip” (Figure 11B). In addition, the distance of each gap to the anterior chamber and to the epithelial surface was quantified. Distance to the anterior chamber was drawn by extending a line from the gap parallel to the keratoprosthesis stem and intersecting the back plate. Distance to the epithelial surface was measured by extending a line from the gap tangent to the keratoprosthesis front plate and intersecting the epithelial surface. Measurements were recorded by two blind observers (CMG and EVT), and the average of the two measurements was used in analysis. Images were also reviewed and confirmed for accuracy by a third observer (AC). All results were considered statistically significant when the p-value was less than 0.05. Stata 11.2 (College Station, Texas) was used for statistical analysis.

RESULTS

Out of 346 patients analyzed above, 43 cases of vitreous inflammation were identified. Patients with positive cultures, or with a known cause for vitreous inflammation (such as immediate postoperative inflammation, vitreous hemorrhage, infectious keratitis, trauma, or leak) were then excluded from further analysis. Of the remaining 23 keratoprosthesis patients – those defined as having idiopathic vitreous inflammation – fourteen could be recruited to the case-control study. These fourteen patients were imaged with AS-OCT with RTVue Optovue OCT® (Fremont, CA). The patients analyzed in this case-control study were all reviewed previously (above). Of the 14 patients imaged, 13 had a type I keratoprosthesis and one had a type II keratoprosthesis. Eyelid skin in the single patient with a type II keratoprosthesis did not permit visualization of the corneal-keratoprosthesis interface, and this patient was excluded from further analysis. The 13 patients with a type I device were compared with 34 control keratoprosthesis type I recipients with no history of sterile vitritis.
Using AS-OCT, we obtained high-resolution images of the keratoprosthesis, seen as a T-shaped cylinder with grooved sides through the center of the cornea donor tissue. The bandage contact lens, front plate, optical cylinder, back plate, corneal graft, and the graft–host junction were clearly seen in the images obtained (Figure 11A).

Demographic and clinical characteristics of the 13 study subjects with a type I keratoprosthesis and idiopathic vitreous inflammation are presented in Table 2. Seven of 13 patients were male. The average age of patients was 58.7 years (range 26-72 yrs). Eight of 13 eyes were aphakic. Preoperative diagnoses included graft failure (10), trachoma (1), corneal ulcer (1) and anirida (1). Thirty-four controls (34 eyes) with no history of vitreous inflammation after keratoprosthesis were imaged using AS-OCT. These served as controls. Twenty were male. The average age of patients in this cohort was 61.2 years (range 60-90 yrs). 22/34 eyes were aphakic. Preoperative diagnoses were consistent with the typical preoperative indications for a keratoprosthesis (Figure 6). The difference in ages between cases and controls was not statistically significant.

The 13 cases presented with idiopathic vitreous inflammation an average of 4.2 years after surgery (range 6 months -14.4 years). The mean single postoperative time point of AS-OCT imaging was 3.6 years (range 1.9 - 14.2 years). Eleven of 13 patients had at least one gap on AS-OCT (84.6%). The average number of gaps in this cohort was 2.6 (SD 1.6). The average size of these gaps was 0.056 mm² (SD 0.049). For the 34 controls, the mean single postoperative time point of AS-OCT imaging was 3.5 years (range 3 months - 13.8 years). 11/34 patients (32.3%) had at least one gap on AS-OCT. The average number of gaps in this cohort was 0.5 (SD 0.8). The average size of these gaps was 0.039 mm² (SD 0.025). Data is depicted in Table 3.

There was no statistically significant difference in time from keratoprosthesis surgery to AS-OCT imaging between cases and controls (p=0.54). There was a statistically significant difference in the proportion of patients presenting with at least 1 gap on AS-OCT between cases and controls (p=0.0008). Amongst the patients that presented with gaps, there was a significant difference in the number of gaps between cases and controls (p< 0.0001). Amongst the patients who had gaps, there was no significant difference in the size of the gaps between cases and controls (p-value = 0.36). Patients with gaps on OCT were 12.5 times more likely to have an associated history of sterile vitritis than patients with no gaps on OCT (odds ratio 12:55, p=0.003, 95% CI [2.3, 66.0], Table 3).
In patients with sterile vitritis and gaps on OCT, 61.1% of gaps were under the front plate. There was no statistically significant difference between cases and controls with respect to the distance between the gap and the epithelial surface (1287.4 ± 591.6 vs. 1147 ± 1159.3; p=0.73), between the gap and anterior chamber (465.88 ± 138.5 vs. 554.7 ± 215; p=0.25), or with respect to the presence of an epithelium lip over the front plate (76.9% vs. 76.5%; p=0.82). There was also no statistical difference in number of gaps on OCT between eyes with a titanium or polymethylmethacrylate (PMMA) back plate (p= 0.41), or for aphakic versus pseudophakic eyes (p=0.34). The presence of retroprosthetic membranes was also not associated with a statistically significant difference in number of gaps on OCT (p=0.52).

**DISCUSSION**

AS-OCT is an important imaging modality for evaluating anterior segment anatomy in keratoprosthesis patients. Only a few papers in the literature have addressed tissue gaps (Garcia 2010, Fernandez 2012, and Shapiro 2013). Garcia et. al documented 2 gaps in 15 keratoprosthesis eyes, using AS-OCT. Fernandez et. al quantified gaps using AS-OCT in the vertical meridian only. Shapiro et. al identified gaps in 8/26 eyes, using AS-OCT. 22 months was the farthest follow-up time for these studies. For our study, we chose to evaluate the area of corneal tissue loss at the graft-keratoprosthesis junction. While the number of patients who develop sterile vitritis is small (23/346 patients between 2000-2013 at Massachusetts Eye and Ear Infirmary), our study successfully captured 14 patients. While we have noted an association between cornea periprosthetic tissue loss and idiopathic vitreous inflammation using anterior segment OCT, we could not test causality in a retrospective study.

The etiology of sterile vitritis is unclear. Microbial components or debris could enter the inside of the eye and trigger non-infectious inflammation, or this could reflect a systemic immune response with ocular manifestations, such as in primary uveitis.

Micromotion of other prosthetic devices, such as dental implants, have been shown to induce sterile inflammation (Gratton 2001). This generates chronic leukocyte recruitment and excessive production of matrix metalloproteinases causing the pathological breakdown of surrounding host tissues (Emecen-Huja 2013). A similar process could be occurring with the
Boston keratoprosthesis. Micromotion of the KPro, could occur through lid or globe movement, or through increased intraocular pressure generating an uneven force distribution on the device (Barber 2011). These processes could induce sterile inflammation, stimulate the excessive production of matrix metalloproteinases, and cause breakdown of surrounding corneal tissue. These areas of corneal tissue loss (“gaps”) could become an entry point for components of bacteria, or inorganic debris, from the outside world (Zimmerli 2011). This mechanism could only occur upon tissue remodeling around the keratoprosthesis, perhaps explaining why the complication occurs months to years after implantation.

Garcia et al. showed that despite the evidence of gaps along the keratoprosthesis-donor interface in several patients, the device continues to be stable long-term (Garcia 2010). Moreover, increased incidence of endophthalmitis or aqueous leak have not been reported in these cases (Garcia 2010). However, according to the data presented above (namely, the association that patients with gaps on OCT are 12.5 times more likely to have a history of sterile vitritis than patients with no gaps on OCT), we propose that gaps could be a risk factor for episodes of idiopathic vitritis. In several cases, idiopathic vitritis has been shown to threaten long-term visual prognosis.

Keratoprosthesis is a relatively uncommon surgical intervention, and sterile vitritis is a relatively uncommon complication. Therefore, a small sample size could not be avoided. Further work will involve imaging patients prospectively at regular intervals to see if these gaps increase in size long-term or cause further sequelae. Such findings will have important implications for clinical management.
SUMMARY

Although there are often obvious causes of vitreous inflammation after keratoprosthesis, many cases have no identifiable trigger. This thesis offers new insight into the disorder, demonstrating that the classical paradigm for sterile vitritis after keratoprosthesis implantation (sudden, painless loss of vision with full recovery of vision upon treatment with periocular steroids) only applies to a subset of episodes. Sterile vitritis in fact shows a wide spectrum of presentation. Presentation can mimic infectious endophthalmitis yet be culture negative. The clinician should be aware of the potential for an inexorably slow resolution of vitritis despite corticosteroid treatment and that full recovery of baseline BCVA is not guaranteed. Sterile vitritis is not harmless and can diminish long-term vision. A vitreous biopsy with injection of intraocular antibiotics is still recommended when clinical signs and symptoms suggest infectious endophthalmitis, to avoid risk of loss of the eye from an untreated infection.

We developed a case-control study to investigate further one potential mechanism for sterile vitritis, that of an opening between the KPro donor interface and adjacent donor cornea tissue. Findings demonstrated that the KPro–donor cornea interface can be accurately seen and quantified on AS-OCT in KPro type I patients. While this potential space may not affect the structural integrity of the assembled device, gaps on OCT could serve as entry points for debris or bacterial components, triggering inflammatory mediators. This may constitute an important cause for idiopathic vitreous inflammation in keratoprosthesis patients. Further studies will be needed to assess the etiology of these gaps. This work has shown that AS-OCT imaging is important to include in the standard post-operative evaluation of keratoprosthesis recipients. This imaging is now becoming a fundamental part of the standard of care for these patients at Massachusetts Eye and Ear Infirmary and at other institutions.

Further work may include comparing the vitreous fluid from sterile vitritis patients with KPros to vitrectomy patients without KPros. We could test for endotoxin by widely available assays and bacterial nucleic acid by polymerase chain reaction. Since the number of patients with new episodes is sporadic, and the sample size small, such a project will require continued long-term follow-up.

This improved understanding of sterile vitritis has directed clinical management and may influence potential changes to the device design. In addition, this work has furthered the use of
anterior segment OCT in providing information about the assimilation of the keratoprosthesis into surrounding corneal tissue. Given this data, the continued use of AS-OCT imaging is valuable in an effort to further elucidate the pathophysiology of sterile vitritis. This imaging can help identify those at risk not only for sterile vitritis but potentially for other complications related to keratoprosthesis placement, such as retroprosthetic membranes, glaucoma, and infectious endophthalmitis. Understanding the origin of sterile vitritis may help explain other adverse inflammatory changes seen after Boston KPro placement, as described above. This understanding is fundamental to the goal of making such complications after KPro implantation truly rare.
REFERENCES


# Tables and Figures

## Table 1. Characteristics of Patients with Idiopathic Vitreous Inflammation after Keratoprosthesis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>History of Auto-Immune Disease</th>
<th>Pre-Operative Corneal Diagnosis</th>
<th>Symptoms</th>
<th>Pre-Episode Topical Medications</th>
<th>VA before episode</th>
<th>VA at episode</th>
<th>Time Since Surgery</th>
<th>Tap/Result</th>
<th>Treatment beyond eye drops</th>
<th>Weeks to clear vitreous</th>
<th>Best Post Episode VA/weeks to best vision</th>
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<tr>
<td>1</td>
<td>HZO</td>
<td>Painful, sudden VA</td>
<td>Latanoprost, Cosopt, Moxifloxacin, PF</td>
<td>20/40</td>
<td>LP</td>
<td>2.3 months</td>
<td>No</td>
<td>RT Tri</td>
<td>7.6</td>
<td>20/100</td>
<td>7.6 wks</td>
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<td>2</td>
<td>Yes</td>
<td>SJS</td>
<td>Vanco, Gatifloxacin, Moxifloxacin, Provera</td>
<td>HM</td>
<td>HM (++)</td>
<td>8.5 yrs</td>
<td>No</td>
<td>RT Tri</td>
<td>24.6</td>
<td>NLP N/A</td>
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<td>3</td>
<td>Trachoma, HSV Keratitis</td>
<td>Painful, sudden VA</td>
<td>Moxifloxacin, PF Latanoprost Run out of Vanco for past 2 months</td>
<td>20/400 (++)</td>
<td>20/400 (++)</td>
<td>1.15 yrs</td>
<td>Yes, Neg.</td>
<td>RT Tri</td>
<td>10.9</td>
<td>20/400</td>
<td>2.3 wks</td>
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<td>Trachoma, HSV Keratitis</td>
<td>Painful, sudden VA</td>
<td>PF, Gatifloxacin, Moxifloxacin, Polytrim</td>
<td>20/60</td>
<td>20/400 (++)</td>
<td>7.9 yrs</td>
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<td>6 days</td>
<td>20/100</td>
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<td>Vanco, Moxifloxacin, Brimonidine missed last dose of remicade</td>
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<td>20/200 (++)</td>
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<td>20/700</td>
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<td>4</td>
<td>Yes</td>
<td>SJS</td>
<td>Vanco, Moxifloxacin, Brimonidine missed last dose of remicade</td>
<td>20/50-1</td>
<td>20/100 (++)</td>
<td>2.4 months</td>
<td>No</td>
<td>Choroidal drainage</td>
<td>14</td>
<td>20/400</td>
<td>14 wks</td>
</tr>
<tr>
<td>5</td>
<td>Graft failure (Reiger’s syndrome)</td>
<td>Paintless, gradual VA, photophobia, flashes</td>
<td>Prednisolone Gatifloxacin Vanco Cosopt</td>
<td>20/200-20/300</td>
<td>HM w/o direction</td>
<td>5 days</td>
<td>Yes, Neg.</td>
<td>RT Tri Cefaz. + Vanco inj. RT Tri</td>
<td>6.1</td>
<td>20/300</td>
<td>2 wks</td>
</tr>
<tr>
<td>6</td>
<td>Graft failure</td>
<td>Fluctuating pain, gradual VA, redness</td>
<td>Prednisolone Moxifloxacin Cosopt Moxifloxacin PF</td>
<td>20/200-20/300</td>
<td>CF @ 3 ft.</td>
<td>29.2 months</td>
<td>No</td>
<td>Lost to follow-up</td>
<td>CF at 6 ft. 1 day later, then lost to follow up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Corneal scarring (trachoma)</td>
<td>Paintless, gradual VA, redness, tearing</td>
<td>PF, Moxifloxacin, Brimonidine, Systane</td>
<td>20/200-20/300</td>
<td>CF at 3 ft.</td>
<td>6.7 months</td>
<td>No</td>
<td>RT Tri</td>
<td>16.4</td>
<td>20/200-1</td>
<td>16.9 wks</td>
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<tr>
<td>8a</td>
<td>Graft Failure</td>
<td>Paintless, gradual VA, redness, tearing</td>
<td>PF Zymar, Vanco Cosopt</td>
<td>20/200-1</td>
<td>CF at 3 ft.</td>
<td>6.7 months</td>
<td>No</td>
<td>RT Tri</td>
<td>16.4</td>
<td>20/200-1</td>
<td>16.9 wks</td>
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<tr>
<td>8b</td>
<td>Graft Failure</td>
<td>Paintless, gradual VA, redness, tearing</td>
<td>PF Zymar, Vanco Cosopt</td>
<td>20/200</td>
<td>HM</td>
<td>5.0 months</td>
<td>No</td>
<td>RT Tri</td>
<td>21.3</td>
<td>20/100</td>
<td>24.9 wks</td>
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<td>8c</td>
<td>Graft Failure</td>
<td>Paintless, sudden VA, redness, tearing</td>
<td>PF Zymar, Vanco Cosopt</td>
<td>20/200-20/300</td>
<td>CF at 0.5 ft.</td>
<td>7.6 months</td>
<td>No</td>
<td>RT Tri</td>
<td>33.6</td>
<td>20/50</td>
<td>13 wks</td>
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<tr>
<td>9a</td>
<td>Graft Failure (end.decomp)</td>
<td>Painful, sudden VA, redness, tearing</td>
<td>PF Gatifloxacin, brimonidine, Systane</td>
<td>20/30-2</td>
<td>20/400 (++)</td>
<td>8.4 months</td>
<td>Yes, Neg.</td>
<td>RT Tri</td>
<td>33.6</td>
<td>20/50</td>
<td>13 wks</td>
</tr>
<tr>
<td>9b</td>
<td>Graft Failure (end.decomp)</td>
<td>Unknown (#)</td>
<td>PF Zymar, Alphagan</td>
<td>20/60 (++)</td>
<td>(#)</td>
<td>19.3 months</td>
<td>Yes, Neg.</td>
<td>RT Tri</td>
<td>20 wks</td>
<td>20/30 (##)</td>
<td>20 wks</td>
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<tr>
<td>9c</td>
<td>Graft Failure (end.decomp)</td>
<td>Paintless, gradual VA, redness, tear, discharge</td>
<td>PF Zymaxid, Alphagan, Vanco Cosopt</td>
<td>20/30 (##)</td>
<td>(#)</td>
<td>29.9 months</td>
<td>No</td>
<td>RT Tri</td>
<td>4.7 wks</td>
<td>20/40 (##)</td>
<td>4.7 wks</td>
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<tr>
<td>10</td>
<td>Graft Failure</td>
<td>Painful, gradual VA, redness</td>
<td>Cellcept, Gatifloxacin, Tacrolimus</td>
<td>20/150</td>
<td>CF 6 in.</td>
<td>17.9 months</td>
<td>No</td>
<td>RT Tri</td>
<td>Developed RD 2 wks later</td>
<td>20/300</td>
<td>9.7 wks</td>
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<tr>
<td>No.</td>
<td>Description</td>
<td>VA, Symptoms</td>
<td>Medications</td>
<td>Follow-up</td>
<td>Comments</td>
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<tr>
<td>11</td>
<td>Aniridic keratopathy</td>
<td>VA, floaters and redness</td>
<td>Brinzolamide, Prednisolone, Vigamox, Polytrim, Cyclosporine</td>
<td>20/300 20/300</td>
<td>6.1 months No RT Tri</td>
<td>17 20/150 10 wks</td>
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<td></td>
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<tr>
<td>12</td>
<td>Severe corneal opacities</td>
<td>Painful, gradual VA, redness</td>
<td>PF, Ofloxacin</td>
<td>HM LP</td>
<td>52 days No RT Tri</td>
<td>36.7 CF at 1 ft. 36.7 wks</td>
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<td>13</td>
<td>Yes SJS</td>
<td>Painless, sudden VA, floaters, redness</td>
<td>Brimonidine, Brinzolamide, Vancom, Mozifloxacin</td>
<td>CF 6 ft. (##)</td>
<td>48.2 months No</td>
<td>2 days CF 6 ft. 2 days</td>
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<tr>
<td>14</td>
<td>Yes SJS</td>
<td>VA, sudden onset of floaters</td>
<td>Vancom, Tobramycin, Acetazolamide</td>
<td>20/20-1 20/20-2</td>
<td>12 months No RT Tri</td>
<td>3.1 20/20-1 1 wk</td>
<td></td>
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<tr>
<td>15a</td>
<td>Graft failure (trauma)</td>
<td>Painful, gradual VA, redness, tearing</td>
<td>PF, Gatifloxacin, Vancom, Timolol</td>
<td>20/60+2</td>
<td>2.5 months No RT Tri</td>
<td>9.3 20/30+2 21.3 wks</td>
<td></td>
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<tr>
<td>15b</td>
<td>Graft failure (trauma)</td>
<td>Painless, gradual VA, redness, tearing</td>
<td>PF, Timolol, Polytrim, Acyclovir</td>
<td>20/40 20/125</td>
<td>13.9 months No RT Tri</td>
<td>Never cleared 20/300 8.9 wks</td>
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<tr>
<td>15c</td>
<td>Graft failure (trauma)</td>
<td>Painless, sudden VA, floaters</td>
<td>PF, Polytrim, Vancom, Timolol, Acyclovir (ran out 3 days ago)</td>
<td>20/300 20/400</td>
<td>27.4 months No RT Tri</td>
<td>23.8 20/125 35.9 wks</td>
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<td>16</td>
<td>Repeat graft failure (chemical burn)</td>
<td>Fluctuating pain, gradual VA, redness, tearing</td>
<td>PF, Vancom</td>
<td>20/50+2</td>
<td>8.9 months Yes, Neg. RT Tri</td>
<td>9.1 20/60+2 6 days</td>
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<td>17a</td>
<td>Repeat graft failure (Fuch’s)</td>
<td>Painless, sudden VA, photophobia</td>
<td>PF, Ketorolac, Ofloxacin, cyclopentolate, Timolol</td>
<td>20/100-1 20/300</td>
<td>3.5 months Yes, Neg. RT Tri</td>
<td>2.6 20/80+1 21.6 wks</td>
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<tr>
<td>17b</td>
<td>Repeat graft failure (Fuch’s)</td>
<td>Painless, gradual VA, floaters</td>
<td>Azopt, Pred Forte, Ocuflex, Pred Mild, Patanol</td>
<td>20/60 20/80</td>
<td>4.4 yrs No</td>
<td>7.6 20/60 2.6 wks</td>
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<tr>
<td>18a</td>
<td>Yes Repeat graft failure (KCN)</td>
<td>Painless, sudden VA, floaters</td>
<td>Vancom, Mozifloxacin, Latanoprost, Acetazolamide</td>
<td>20/50+2</td>
<td>4.6 yrs Yes, Neg. RT Tri</td>
<td>36.4 20/30-2 23.4 wks</td>
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<tr>
<td>18b</td>
<td>Yes Repeat graft failure (KCN)</td>
<td>Painful, sudden VA, redness and mild swelling</td>
<td>Pred Forte, Vancomycin, Polytrim, Xalatan, Diamox, Patanol</td>
<td>20/30</td>
<td>10.5 yrs Yes, Neg. RT Tri</td>
<td>14.4 20/30 14.4 wks</td>
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<tr>
<td>18c</td>
<td>Yes Repeat graft failure (KCN)</td>
<td>Painless, sudden VA, redness and mild swelling</td>
<td>PF, Vancom, Timov, Xalatan, Diamox, Patanol</td>
<td>20/30</td>
<td>13.3 yrs No</td>
<td>7 20/30 7 wks</td>
<td></td>
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<td>19</td>
<td>Yes Chronic uveitis</td>
<td>Pain on EM, sudden VA</td>
<td>Vancom, mozifloxacin, PF</td>
<td>HM LP</td>
<td>1.9 yrs Yes, Neg.</td>
<td>4.3 LP N/A</td>
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<td>20a</td>
<td>Repeat graft failure</td>
<td>Painless, gradual VA, floaters</td>
<td>Gatifloxacin, PF Ketorolac timoptic</td>
<td>20/80 20/200</td>
<td>9.0 months No</td>
<td>2 20/100 56 wks</td>
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<tr>
<td>20b</td>
<td>Repeat graft failure</td>
<td>Painless, sudden VA, floaters</td>
<td>Gatifloxacin, PF Trimoptic</td>
<td>20/150</td>
<td>5.7 months No</td>
<td>15 20/100 16.6 wks</td>
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<tr>
<td>20c</td>
<td>Repeat graft failure</td>
<td>Painless, sudden VA, floaters</td>
<td>Ofloxacin, PF Timoptic</td>
<td>20/100</td>
<td>1.2 years No</td>
<td>28.7 20/60 28.7 wks</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>21a</td>
<td>HZO</td>
<td>Painless, sudden VA, redness</td>
<td>Gatifloxacin PF</td>
<td>20/80</td>
<td>HM</td>
<td>2.9 months</td>
<td>Yes, Neg.</td>
<td>RT Tri</td>
<td>56</td>
<td>20/80</td>
<td>23 wks</td>
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<tr>
<td>21b</td>
<td>HZO</td>
<td>Painless, sudden VA, Floaters</td>
<td>Moxifloxacin PF Vanco</td>
<td>20/80</td>
<td>20/400</td>
<td>11 months</td>
<td>Yes, Neg.</td>
<td>RT Tri</td>
<td>9.3</td>
<td>20/80</td>
<td>3.3 wks</td>
</tr>
<tr>
<td>21c</td>
<td>HZO</td>
<td>Painless, sudden VA, Floaters</td>
<td>Moxifloxacin PF Vanco</td>
<td>20/80</td>
<td>CF at 1 ft.</td>
<td>.3 years</td>
<td>No</td>
<td>RT Tri</td>
<td>2</td>
<td>20/100</td>
<td>8 wks</td>
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<tr>
<td>21d</td>
<td>HZO</td>
<td>Painless, sudden VA, Floaters</td>
<td>Moxifloxacin PF Vanco</td>
<td>20/100</td>
<td>CF at 5 ft.</td>
<td>1.7 years</td>
<td>No</td>
<td>RT Tri</td>
<td>2.7</td>
<td>20/100</td>
<td>2.7 wks</td>
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<tr>
<td>21e</td>
<td>HZO</td>
<td>Painless, sudden VA, Floaters</td>
<td>Moxifloxacin PF Vanco</td>
<td>20/100</td>
<td>CF at 3 ft.</td>
<td>1.9 years</td>
<td>No</td>
<td>RT Tri</td>
<td>4.4</td>
<td>20/80</td>
<td>4.4 wks</td>
</tr>
<tr>
<td>21f</td>
<td>HZO</td>
<td>Painless, sudden VA, Floaters</td>
<td>Moxifloxacin PF Vanco</td>
<td>20/80</td>
<td>(*#)</td>
<td>2.5 years</td>
<td>No</td>
<td>RT Tri</td>
<td>3.3</td>
<td>20/80</td>
<td>2.1 wks</td>
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<tr>
<td>21g</td>
<td>HZO</td>
<td>Painless, sudden VA, No floaters</td>
<td>Moxifloxacin PF Vanco</td>
<td>20/80</td>
<td>20/600</td>
<td>2.8 years</td>
<td>No</td>
<td>RT Tri</td>
<td>2.1</td>
<td>20/100</td>
<td>2.1 wks</td>
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<tr>
<td>22</td>
<td>Repeat Graft Failure (KCN)</td>
<td>Painful, sudden VA, floaters and photophobia</td>
<td>Trim/Polym. PF Ketorolac</td>
<td>20/125</td>
<td>20/100</td>
<td>4.9 months</td>
<td>Yes, Coag Neg. staph</td>
<td>RT Tri</td>
<td>2</td>
<td>20/125 (++++)</td>
<td>2 wks</td>
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<tr>
<td>23a</td>
<td>Repeat Graft Failure (KCN)</td>
<td>Painful, sudden VA</td>
<td>Gatifloxacin PF Timoptic Cyclopentolate</td>
<td>20/200</td>
<td>HM</td>
<td>3.8 months</td>
<td>Yes, Neg.</td>
<td>8.6</td>
<td>20/200</td>
<td>33.6 wks</td>
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<tr>
<td>23b</td>
<td>Repeat Graft Failure (KCN)</td>
<td>Painful, sudden VA, sensation of pressure</td>
<td>Gatifloxacin PF Vanco Timoptic Cyclopentolate</td>
<td>20/200</td>
<td>LP</td>
<td>8.9 months</td>
<td>Yes, Neg.</td>
<td>PPV</td>
<td>13.1</td>
<td>20/200</td>
<td>13.1 wks</td>
</tr>
</tbody>
</table>

Repeated episodes in the same patient are denoted by a letter (a, b, c)
SJS= Stevens-Johnson Syndrome
Vanco=vancomycin
HZO= Herpes Zoster Ophthalmicus
OCP= ocular cicatricial pemphigoid
PF=predforte
ACV= acyclovir
KCN=keratoconus
RT Tri= retrotenons triamcinolone acetate
PPV= pars plana vitrectomy
end.decomp= endothelial decompensation
Trim/Polym.= Trimethoprim/polymxin
Ceftaz.= ceftazidine
Table 2: Demographic data of patients imaged using anterior segment OCT.

<table>
<thead>
<tr>
<th></th>
<th>Controls (no. = 34)</th>
<th>Cases (no. = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>58.7 years (range 26-72)</td>
<td>61.2 years (range 60-90)</td>
</tr>
<tr>
<td><strong>% Male</strong></td>
<td>7/13 = 53.8%</td>
<td>20/34 = 58.8%</td>
</tr>
<tr>
<td><strong>% Aphakic</strong></td>
<td>8/13 = 61.5%</td>
<td>22/34 = 64.7%</td>
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</table>

Table 3: Comparison of gap measurements with AS-OCT for keratoprosthesis eyes with and without a history of sterile vitritis.

<table>
<thead>
<tr>
<th></th>
<th>Controls (no. = 34)</th>
<th>Cases (no. = 13)</th>
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<tbody>
<tr>
<td><strong>Follow-up time</strong></td>
<td>42.5 ± 42.4 months</td>
<td>51.1 ± 48.1 months</td>
</tr>
<tr>
<td><strong>Presence of gaps</strong></td>
<td>11/34 = 32%</td>
<td>11/13 = 86% *</td>
</tr>
<tr>
<td><strong>Number of gaps</strong></td>
<td>0.5 ± 0.8 (range 0-4)</td>
<td>2.6 ± 1.6 * (range 0-4)</td>
</tr>
<tr>
<td><strong>Size of gaps</strong></td>
<td>0.039 ± 0.025 mm²  (range 0.009-0.188)</td>
<td>0.056 ± 0.049 mm² (range 0.012-0.274)</td>
</tr>
<tr>
<td><strong>Distance gap-surface</strong></td>
<td>1147.0 ± 1159.3μm</td>
<td>1287.4 ± 591.6 μm</td>
</tr>
<tr>
<td><strong>Distance gap to anterior chamber</strong></td>
<td>554.7 ± 215.0 μm</td>
<td>465.88 ± 138.5 μm</td>
</tr>
</tbody>
</table>

* = statistically significant
FIGURE 1. (A) Photograph of the Boston keratoprosthesis. (B) Photograph of a patient’s left eye after implantation of the Boston keratoprosthesis. Visual acuity 2 years after implantation was improved from hand motions to 20/25. Courtesy James Chodosh MD, MPH

FIGURE 2. These complications of the keratoprosthesis are well-documented in the literature. Images: [http://archopht.jamanetwork.com/data/Journals/OPHTH/10235/ecs05081f1.png](http://archopht.jamanetwork.com/data/Journals/OPHTH/10235/ecs05081f1.png) [http://www.nature.com/eye/journal/v22/n10/fig_tab/eye200851f6.html](http://www.nature.com/eye/journal/v22/n10/fig_tab/eye200851f6.html)
FIGURE 3. (A) Vitreous cells seen at the slit lamp in a patient presenting with sudden and painless loss of vision with no extra ocular symptoms. Note the appearance of dust-like particles in the width of the slit beam, suggestive of vitreous cells. (B) Patient above presented with a red, tearing, and painful eye, mimicking infectious endophthalmitis. However, cultures showed no growth.

FIGURE 4. A Schematic of the Boston Keratoprosthesis. Note the position of the corneal graft tissue sandwiched between the front and back plates of the prosthesis. Image: http://eyeworld.org/images/New_Articles/2007/05/32.jpg
FIGURE 5. All causes of vitreous inflammation in keratoprosthesis recipients. The tree diagram represents all patients presenting with vitreous cells on slit-lamp examination, at any point after Boston keratoprosthesis implantation.

FIGURE 6. Preoperative diagnoses of 23 patients receiving a Boston keratoprosthesis who later presented with idiopathic vitreous inflammation. SJS, Stevens–Johnson syndrome.
FIGURE 7. Photomicrograph of a patient’s eye with culture-negative vitreous inflammation, who presented with conjunctival injection, tearing and discomfort, mimicking infectious endophthalmitis. The patient’s keratoprosthesis was performed for multiple failed corneal transplants secondary to Fuchs’ endothelial dystrophy, and was five years postoperative at the time of the photograph.
FIGURE 8. Graph depicting the mean change in BCVA throughout the course of sterile vitritis episodes. Time from the examination just before the onset of sterile vitritis and time from the 3-week examination to resolution was variable. The mean time between baseline measurement of best-corrected vision and presentation with sterile vitritis was 1.6 months. The mean time between presentation and resolution of vitritis was 2.2 months. Note that vision was not recorded at all time points for all patients. Approximately 80% of patients recovered to within 2 Snellen lines of baseline vision. SE, standard error.
FIGURE 9. Proposed algorithm for clinical management of post keratoprosthesis vitritis without an obvious cause. Note that failure to respond to either regional corticosteroids or intraocular antibiotics (with negative smears and cultures) may require a change of therapy to intraocular antibiotics or regional corticosteroids, respectively.
FIGURES 10A and 10B. Using AS-OCT, 4 quadrants around the stem can be imaged, as shown in Figure 10A (360 degree circumference of Kpro-corneal tissue interface). Images were analyzed in raster mode (Figure 10B). Raster mode provides 17 images/quadrant, with a 250 micrometer distance between each image.
FIGURE 11A.

FIGURE 11B.
FIGURES 11A, B, and C. (A) Image of a keratoprosthesis type I with evidence of peri-prosthetic corneal tissue loss under the front plate and abutting stem (combined gap), in a patient with a history of repeated sterile vitritis. BCL=bandage contact lens. (B) AS-OCT of a combined gap in a patient with a history of sterile vitritis. Note the presence of epithelial tissue extending over the front plate. (C) AS-OCT of a front plate gap in a patient with a history of sterile vitritis.