Review Article

Boston type I keratoprosthesis

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Abstract: Successful corneal solid tissue transplantation, beginning with penetrating keratoplasty (PKP), and evolving to include contemporary lamellar and endothelial keratoplasty, has been a tremendous advancement in the struggle to combat corneal blindness. However, there remain patients with high-risk features predictive of transplant failure, for whom donor keratoplasty is not a viable option. Prosthetic corneas have therefore been developed in order to meet the needs of these patients. The Boston type I keratoprosthesis (BKPro) is the most widely used prosthetic cornea in the treatment of corneal blindness. In the years since the BKPro's introduction, refinement of surgical technique and clinical management as well as improvements in prosthetic design have contributed to promising patient outcomes, particularly in the short term. As such, patients with keratoprosthesis implants continue to grow in number, and the indications for the BKPro have commensurately increased. However, risks of permanently blinding complications after implantation persist over all stages of follow-up. For the foreseeable future, the success of keratoprosthesis (KPro) implantation will continue to depend on refined patient selection, preoperative optimization, and incisive postoperative management. Here we explore indications, surgical technique and postoperative outcomes as well as several core tenants in the management of BKPro patients: limiting glaucomatous progression, controlling inflammation, and optimizing the ocular surface. The exquisite sensitivity of the BKPro-implanted eye to perturbations in any one of these areas showcases the intimate relationship between the prosthetic device and its surrounding environment.

Keywords: Keratoprosthesis; corneal transplant; Boston type I keratoprosthesis (BKPro); keratoprosthesis (KPro)

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Introduction

While the concept of an artificial corneal prosthesis was first formally introduced in the medical literature in the late 1700s (1), the technique only became feasible in the last 50 years with advances in antimicrobial and transplant medicine. While donor keratoplasty remains the first-line approach for many patients, a number of clinical scenarios place patients at high risk for donor graft rejection or failure, either due to a history of exposure to multiple previous failed donor grafts or due to an underlying pathology for corneal blindness associated with a high rate of primary failure, such as conditions associate with limbal stem cell deficiency or ocular autoimmune disorders. Because of the prevalence of these clinical scenarios where outcomes of donor keratoplasty remain poor, there exists a need for graft options which retain optical clarity despite an ocular environment that is inadequate to support a biologic graft. In an attempt to better address this need, the Boston type I keratoprosthesis (BKPro) was developed by Professor Claes Dohlman at the Massachusetts Eye and Ear Infirmary (MEEI) and presented in a case series in 1974 (2). The BKPro was approved for clinical use in the treatment of severe corneal opacity in the United States by the Food

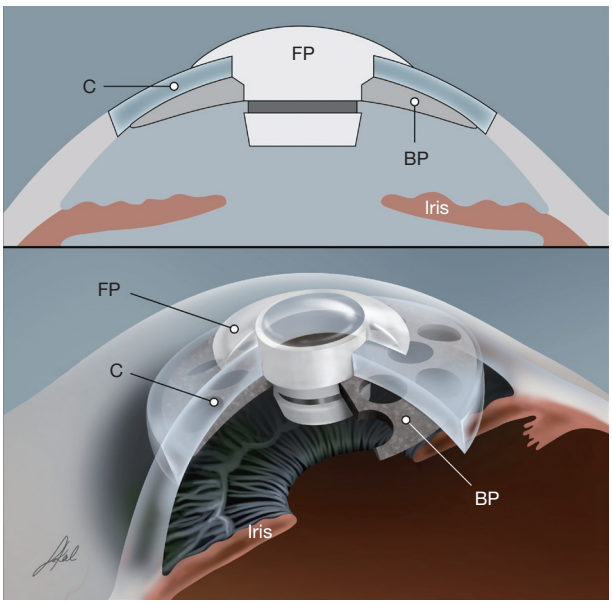

Figure 1 Boston type I keratoprosthesis design. FP, front plate; BP, back plate; C, donor cornea.

and Drug Administration in 1992. While an increasing number of keratoprosthesis designs are currently in use and development (3), the BKPro remains the most commonly used artificial cornea (4) with the number implanted approaching 20,000 worldwide. This is in large part due to progressive advancements in prosthetic design, surgical technique, and clinical management which have decreased the rate of complications and improved the risk-benefit profile of implantation in multiple patient categories (5). BKPro implantation has thus evolved beyond a heroic procedure of last resort and become an option offering a reasonable possibility of long-term functional vision for a variety of patients who are poor candidates for traditional tissue keratoplasty. As a synthetic implant, BKPro does not require an optimized corneal epithelium or functional corneal endothelium in order to maintain optical clarity, and the prosthesis itself is not at risk of melt. While the BKPro does rely on a donor corneal bridge, which can be susceptible to melt and associated complications, in order to maintain continuity with the host eye, the prosthesis design does not require optical clarity from the donor corneal tissue, allowing for a lower burden of support from the host eye. In this way, BKPro can offer functional vision to eyes unable to support the requirements of traditional donor keratoplasty for graft survival with optical clarity. However, the risks of serious and potentially permanently blinding complications associated with BKPro remain relatively high; as such, careful patient selection, optimization, and post-operative management are crucial to a successful BKPro practice. The decisions that we make about who, when, and how revolve around the mechanisms that lead to retentive and visual failure, and our efforts to prevent or mitigate these processes. While addressing the full plethora of possible complications that can occur in BKPros is beyond the scope of this paper, here we would like to focus on the discussion of mechanisms driving glaucomatous progression and sterile keratolysis and approaches to optimization and management to decrease the likelihood of these complications.

Prosthetic design and surgical technique

The BKPro has undergone a number of refinements since it was formally introduced by Dr. Dohlman in 1974. In the current design, the prosthesis consists of an optical stem with a front plate and back plate bracketing a corneal allograft button (*Figure 1*), the latter of which serves as the intermediary between the prosthesis and the host cornea. The front plate is composed of medical-grade polymethylmethacrylate (PMMA), where the radius of curvature of surface determines the optical power of the prosthesis. The BKPro is available in pseudophakic and aphakic powers, the latter of which are specified based on the patient's native axial length. The edges of the front plate are designed in order to optimize continuity between the front plate and the donor cornea and thus minimize mechanical trauma with blinking and eye movement that may destabilize the prosthetic and cause patient discomfort. The central stem connects the front and back plates, extending posteriorly from the front plate as a column that passes through corneal allograft button, into the patient's anterior chamber, where it ends with a flat face that allows transmission of images without distortion. More centrally, the central stem possesses a locking interface where the back plate is secured, just posterior to the donor corneal button. The back plate is available in PMMA or titanium and is fenestrated in order to allow aqueous to reach the donor allograft, an innovation which significantly decreased rates of sterile keratolysis (6). The original back plate design was composed of PMMA and involved screwing the back plate into position at the central stem's locking interface; after several iterations, the current PMMA back plate mounting technique involves the placement of a C-shaped

titanium ring that locks the back plate into position. The newest iteration titanium back plate currently clicks onto the stem without the need for a locking ring. Titanium is non-magnetic and therefore safe for patients undergoing magnetic resonance imaging, and can be anodized to a brown color to help improve cosmesis (7).

Intraoperatively, an appropriate corneal allograft donor size is determined by examining the patient's anterior segment, similar to how one might proceed with a penetrating keratoplasty (PKP). The donor cornea is punched to size; an additional 3-mm trephination is performed centrally with a dermatologic punch. The central stem of the keratoprosthesis is then threaded through the central trephination of the donor cornea, with the corneal epithelium oriented towards the posterior aspect of the front plate attached to the central stem. The back plate is then placed on the stem and pushed along the central stem towards the front plate until it reaches the stem's locking interface, where the back plate is fixed into position, with use of a locking ring if necessary. The patient's native cornea is then trephined and the prosthesis-allograft complex sutured into place.

Indications and patient selection

Due to the mechanical and physiologic systems necessary to retain the prosthesis, the BKPro has been found to be most successful in a wet, blinking eye (8) with minimal inflammation (9). The initial application of the BKPro was to achieve optical clarity in patients with a history of multiple graft failure (5,10). Indeed, this remains the most common indication for BKPro implantation (11), and is a preoperative diagnosis associated with favorable outcomes (9). While the original diagnoses meriting prior corneal transplantation are varied, the performance of this prognostic category likely speaks to the inclusion of disease processes that are non-inflammatory, such as keratoconus, or a history of resolved inflammatory process such as scarring due to prior trauma or infectious keratitis, which have subsequently been found to fare relatively well with BKPro implantation (12). Unsurprisingly, though, increasing number of prior failed grafts at the time of BKPro implantation is successively associated with worse outcomes (12,13). This may correspond to a successively increasing historical burden of cumulative complications due to the underlying disease process and multiple surgical interventions. The decision as to when to transition from PKP to BKPro remains a decision that is individualized to each surgeon and patient. A number of studies show better best-corrected visual acuity (VA) with BKPro as compared to repeat PKP (14,15). One meta-analysis describing an overall BKPro retention rate of 94% and an 80% probability of 20/200 or better VA at 2 years in comparison to 42% probability of 20/200 or better VA at 2 years with repeat PKP, with similar complication rates (13). These numbers represent aggregated results, but echo a long-understood reality that re-graft survival rates, particularly for the third or higher graft, can be quite dismal (16,17).

Given the possibilities that BKPro implantation represents for patients with severe corneal opacity, the procedure has also been extensively explored at this point as the initial keratoplasty procedure in patients whose diagnoses primarily rendered them poor candidates for PKP, such as patients with herpetic keratitis, limbal stem cell deficiency from aniridia, ectodermal dysplasia, chemical injury, or autoimmune disease such as Stevens-Johnson syndrome (SJS) and ocular cicatricial pemphigoid (OCP) (14,18). Of these, patients with SJS and OCP remain notoriously high-risk patients for implantation (9,19-22), whereas patients with chemical burns have fared progressively better as management strategies have improved (23). A recent study reported lower retention of BKPro in cases of primary versus secondary implantation; the authors posit that this may speak to the increased complexity of underlying pathology in patients for whom primary implantation is considered (24). Nevertheless, the implementation of BKPro as a primary penetrating procedure for the treatment of corneal opacity has expanded globally, with a 2012 international survey recording primary BKPro implantation in approximately one-third of study eyes (11). Moreover, as the length of time during which BKPro implants have been utilized globally increases, our expectations regarding longer-term outcomes have grown more refined. *Table 1* shows number of eyes retaining functional vision of 20/200 or better at five years as reported by the most relevant long-term studies available in the literature.

Candidacy for BKPro implantation in patients with unilateral pathology remains controversial, where some practitioners feel that patients with a healthy and sighted contralateral eye should maintain the eye with corneal opacification in reserve such that implantation remains an option in the future (28). With this rationale, the risk of initiating pathological processes leading to permanent blindness are too high compared to the fair likelihood that patients will achieve and sustain adequate vision in the

Table 1 Five-year visual outcomes in eyes with Boston type I keratoprosthesis

Outcomes	Lekhanont, 2014, (25)	Kosker, 2015, (26)	Salvador-Culla, 2016, (23)	Aravena, 2018, (27)	Kanu, 2020, (21)	Szigiato, 2020, (22)
Eyes included (n)	42	37	42	58	111	85
Prognostic categories (%)						
SJS or pemphigoid	19	2.7	0	10.8	5.9	2.4
Chemical or thermal burn	19	10.8	100	16.2	13.2	5.9
Aniridia	0	2.7	0	5.4	20.6	29.4
Other non-cicatrizing	62	83.8	0	67.6	60.3	62.3
Follow-up duration (months, mean ± SD)	64.9±15.2	31.7±21	40.2±24.4	82.8±20.5	90.9±19.7	86.4±15.6
Eyes at 5-year follow-up (n=eyes)	34	8	10	47	68	77
Eyes retaining BCVA ≥20/200 (%)	47.6	63	77	60	75	42

SJS, Stevens-Johnson syndrome; SD, standard deviation; BCVA, best corrected visual acuity.

diseased eye to offer additional functionality. Here again, the decision falls upon the individual surgeon and patient, where candidates of sufficient clinical compatibility who are amenable to and capable of indefinite close follow-up may indeed achieve and sustain adequate vision to justify implantation. One study by the authors of this paper found that there is a significant improvement in quality-of-life after BKPro implantation due to the improvement in vision in the implanted eye, even when the vision in the contralateral eye is better than 20/200, although naturally the magnitude of the improvement is greater in patients who initially had poor vision in both eyes (29). In addition, another study found that stereopsis can be achieved with BKPro implantation and therefore good visual potential in the operated eye as well as preoperative eye alignment are important factors to consider when deciding implantation in the setting of unilateral disease (30). This speaks to the benefit of BKPro implantation. With the regards to the risks, one study interestingly found higher rates of sterile keratolysis and vitritis in BKPro implants in patients with VA >20/200 in the contralateral eye (Group II), with better keratoprosthesis (KPro) survival after the first year in the group that was preoperatively bilaterally blind (Group I) (31). The authors retrospectively found that follow-up was less frequent in Group II patients, and suggest that frequent follow-up played a role in the differential full manifestation of BKPro complications, where heralding signs are often asymptomatic and identified on routine follow-up (32). Notably, the authors of a separate series reporting improved outcomes in BKPro after chemical burns speculate that their success can be attributed to their strict follow-up regimen born from experience (23). This showcases strategies by which motivated patients and practitioners can enjoy success with BKPro implantation, and that falling short of the intensive commitment required can render the risk-benefit profile unfavorable. Similarly, bilateral BKPro implantation in patients with bilateral disease is not advisable, unless the first eye fails to achieve meaningful visual Improvement due to other comorbidities.

Perhaps given the demands of implant maintenance and high complexity of congenital corneal disease, outcomes in pediatric populations remain poor, with high rates of complication, device failure, and permanent vision loss (33). Thus, despite initial hopes that keratoprosthetics devices would allow for rapid improvement of visual axis clarity to promote visual development, BKPro is not typically recommended for pediatric use, and intransigent corneal opacification and the subsequent development of dense amblyopia remains a great challenge in these patients.

Complications and patient optimization

Glaucoma

Glaucoma is the leading cause of permanent visual loss following BKPro implantation (22,34-37). Glaucoma is a common comorbid condition in patients undergoing evaluation for BKPro, with studies describing a prevalence of 61% to 72% prior to BKPro implantation (37), and an incidence of *de novo* glaucoma following implantation from

2% to 60% (21,38-40), with higher rates in the subgroup of patients requiring BKPro removal or exchange (21). Glaucoma progression has been found to progress approximately seven-fold more rapidly in BKPro patients as compared to primary open-angle glaucoma patients (41). Patients with a history of chemical burns seem to be particularly sensitive to even transient increases in intraocular pressure (IOP) (42,43); some authors suggest that such patients retain sequelae of chemical damage extending to the optic nerve, creating durable vulnerability to glaucomatous progression (42). Conversely, cup-to-disk ratio (CDR) progression is the slowest in non-burn, non-autoimmune eyes (41,44), and diagnosis of stromal or endothelial disorders as the indication for BKPro implantation is associated with lower incidence of glaucoma progression, suggesting that non-inflammatory underlying pathology is less likely to extend to angle anatomy or cause anterior segment inflammation (44). The development of elevated IOPs and progression of optic nerve damage in BKPro eyes is understood to be multifactorial, with a component of steroid-response (43) and outflow obstruction via chronic angle closure (45-47), back plate crowding, and the presence of inflammatory debris in the trabecular meshwork (41). Interestingly, some experts have posited that the prosthetic increases scleral rigidity, altering IOP dynamics and leading to glaucoma (48), although this has been difficult to demonstrate. Ocular surface inflammation, implied by the presence of elevated levels of tear film tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), fibroblast growth factor (FGF)-basic, and interferon-gamma (IFN-γ), has been isolated at higher levels in BKPro patients with glaucoma compared to those without (49). Studies using anterior segment optical coherence tomography (AS-OCT) have demonstrated progressive angle-closure in some patients who underwent BKPro implantation (47), leading authors to propose structural prosthetic modifications to decrease adhesion formation. However, anterior chamber depths and the rate of peripheral anterior synechiae (PAS) formation was found to be similar for BKPro back plates sized at 7.0 versus 8.5 mm (49). Previous literature demonstrated that even eyes wherein complete iridectomy had been performed went on to develop glaucoma (33), suggesting that inflammatory alterations and subsequent obstruction of the trabecular meshwork persist on a finer scale than can effectively be rectified by macroscopic positioning of anterior segment structures. Notably, the extent of synechia formation has been found to be significantly higher after secondary BKPro implantation (50), i.e., in patients with a history of prior PKP, likely due to a certain amount of synechial angle closure occurring prior to BKPro implantation (51).

The challenges in diagnosing, monitoring, and treating glaucoma following BKPro implantation are robust and well-documented (38). As such, optimization begins prior to implantation. Low preoperative IOP is a critical protective factor for progression in glaucomatous eyes as well as for glaucoma development in eyes without a pre-existing diagnosis of glaucoma (44); the authors of one recent paper recommend a goal IOP of 12 mmHg, including in patients considered to be non-glaucomatous, prior to proceeding with BKPro implantation. In practice, this can be relatively straightforward to attempt with topical therapy (46); however, the clinician must recall that topical medications have reduced absorption after BKPro and options become limited following implantation due to the altered mechanisms underlying glaucoma in BKPro eyes, where there is little to be gained from increasing trabecular outflow, prostaglandin analogs may be poor options in patients with a history of macular edema or inflammation, and preservative-free formulations are preferred to decrease ocular surface pathology (38).

Beyond topical therapy, staged or concurrent glaucoma drainage device (GDD) implantation in patients without glaucoma is not without risk (52,53), and where the benefits are less clear the decision to proceed must be individualized. We often offer GDD surgery to patients without glaucoma at the time of BKPro implantation.

For patients with a pre-existing diagnosis of glaucoma, the current body of evidence argues in favor of prior or concurrent GDD implantation in patients receiving BKPros. In a recent series, all eyes without surgical intervention for glaucoma had progressive worsening of glaucoma despite IOP that was considered to be adequately controlled preoperatively (54). No consensus exists regarding the optimal timing, but studies have demonstrated that concurrent implantation does not increase the rate of postoperative complications (55). It is typically recommended that the tube be placed in the pars plana following complete vitrectomy in order to mitigate the risk of tube occlusion by anterior segment structures, angle closure, retroprosthetic membrane (RPM) formation, or vitreous (40); of note, completely vitrectomized eyes were generally found to have superior outcomes in one long-term analysis (21). Posterior placement is preferred, with a corneal or corneoscleral patch graft, with lamellar dissection if necessary, to ensure a relatively smooth perilimbal

approach to allow for later contact lens wear. Where timing allows, tube ligation is recommended to optimize watertight conjunctival healing (40). In cases where a diseased ocular surface does not allow for conjunctival closure without tension, a staged reconstructive procedure using amniotic membrane transplant (AMT) with or without mitomycin C, or with a mucosal autograft may allow subsequent GDD placement (56). Unfortunately, there remain patients for whom GDD placement is not possible; moreover, in cicatrizing conjunctival disorders, an impermeable shunt plate capsule can lead to GDD failure (3).

In patients with uncontrolled glaucoma that are poor candidates for GDD or have failed prior surgical therapy trans-scleral cyclophotocoagulation is an option as an adjunct therapy; however, the treatment is difficult to titrate and landmarks are sometimes difficult to identify resulting in the need of frequent re-treatments. Unsurprisingly, as an inflammatory procedure that exerts its effect across the ocular wall, it has been associated with complications including conjunctival dehiscence and fungal endophthalmitis (57). Endocyclophotocoagulation may represent an alternative that spares the conjunctiva and sclera, but which remains pro-inflammatory in nature.

Following BKPro implantation, monitoring becomes classically challenging given the rigid prosthesis optic. Digital palpation remains the gold standard for IOP measurement, with trans-scleral pneumotonometry and Tono-pen in use as supplemental methods. Implantable intraocular telemetric devices for real-time, continuous IOP measurement are in development (40), as well as prototypes integrating these devices into keratoprosthetic implants (58). Humphrey 10-2 static perimetry and Goldmann manual perimetry have been described as reliable and reproducible (58,59); Goldman visual fields are also used to track progression of the disease (60). However, such analyses must naturally exclude those patients who are unable to perform perimetry testing, such as patients with reduced global sensitivity and patients with nystagmus and retinal diseases (49). Optic nerve imaging can be successfully performed through the BKPro optic, but quality of imaging can sometimes be affected and non-mydriatic cameras are recommended. Finally, reliability of optical coherence tomography retinal nerve fiber layer (OCT RNFL) measurements has been demonstrated in some studies (61), others point out the high rate of segmentation errors in patients with BKPros particularly as RNFL thinning increases as reflectivity decreases in cases of greater glaucomatous damage (38). AS-OCT and ultrasound biomicrosopy can be used to evaluate the anterior chamber angle (10). In all, adjunctive testing modalities remain options for which feasibility and reliability vary and must be assessed for the individual BKPro patient given the variability of post-implantation optical behavior.

In general, we recommend close and customized monitoring of the glaucoma status of BKPro patients in order to allow for the prompt recognition of actionable ocular hypertension and glaucomatous damage. BKPro implantation is best done in a setting with a variety of modalities and support for such monitoring. Patients with a pre-existing history of glaucoma or any significant risk factors for development of glaucoma undergo GDD prior or concurrent to BKPro implantation in order to minimize the likelihood that the BKPro patient's visual outcome will ultimately be limited by glaucomatous damage. The GDD tube is best localized to the pars plana, with the patient undergoing vitrectomy in order to preserve the functionality of the tube shunt. Endocyclophotocoagulation remains a late option to be used with caution due to its inflammatory adverse effect profile. We look forward to potential advances in imaging (39) and IOP measurement (61) that would improve our ability to provide glaucoma care for our BKPro patients.

Corneal melting and the ocular surface

Where glaucoma is the leading cause of permanent visual loss following BKPro implantation, sterile keratolysis, or corneal melting, is the principal cause of failure to retain a BKPro (20), and can also lead to hypotony and its associated complications and place the eye at risk for developing superimposed infectious keratitis or endophthalmitis (62). A number of factors contributing to sterile keratolysis have been identified, including decreased donor collar button nutrition and ocular surface desiccation and inflammation. The development of a fenestrated back plate dramatically improved rates of sterile keratolysis from over 50% to approximately 10% in an early comparison (6). RPM formation has also been implicated in obstruction of nutrient delivery to donor tissue, where one study demonstrated the presence of RPM in 100% of eyes with melt in comparison to 34% without melt (63). RPM thickness was also associated with increased risk of sterile keratolysis (63).

There generally exists a negative relationship between the level of chronic inflammation and BKPro surgery outcomes with lower retention rates in patients with underlying

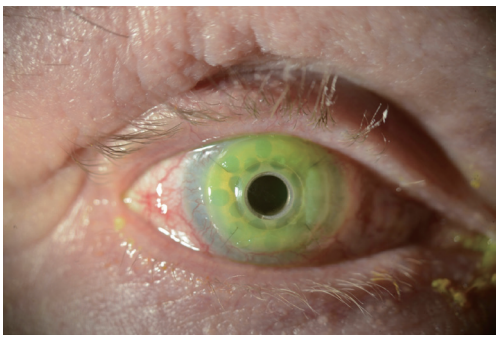

Figure 2 Slit-lamp photograph of a patient with a BKPro implant with surface instillation of fluorescein. The staining pattern demonstrates a circumferential epithelial defect of the donor corneal allograft underlying the BKPro front plate and adjacent to the optic stem. BKPro, Boston type I keratoprosthesis.

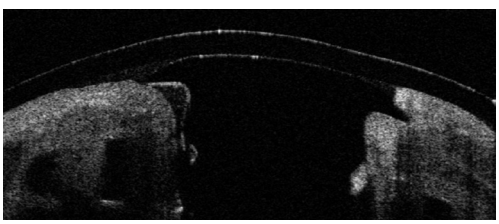

Figure 3 Anterior segment OCT showing a tissue gap in the cornea-optic interface representing early sterile corneal melt. OCT, optical coherence tomography.

ocular surface disease (9,21,27). Particularly in regards to the ocular surface, mechanical stress on the carrier graft has been demonstrated to increase the expression of matrix metalloproteinases (MMP) (62), which may act as or in association with mediators of stromal degradation in sterile keratolysis (64). This mechanical stress is likely present to some extent with normal eye movement, and much more so in patients with abnormal lids (62). Of interest, levels of MMP-13, IL-6, and TNF-α have been shown to increase following eye rubbing in keratoconus patients and have been implicated in the progressive corneal thinning that is a hallmark of the disease (65). Depending on the characteristics of the ocular surface in the individual BKPro eye, surface desiccation and tear hyperosmolarity may also contribute to poor carrier graft health. Persistent epithelial defects (PEDs) represent a risk factor for sterile keratolysis or for infectious keratitis with subsequent corneal melt (32). Of note, PEDs, early sterile keratolysis, and infectious keratitis can often be asymptomatic (23,32). Here, we reiterate the need for frequent routine follow-up. Relatively subtle changes on exam such as the presence of new air bubbles underneath the keratoprosthesis front plate and/or the bandage contact lens can herald interval development and progression of keratolysis. Moreover, we emphasize the need for rigorous adherence to systematic screening and evaluation for new complications at each of these follow-up visits, even if the patient reports doing well and demonstrates stable vision and gross outward appearance. Historically, this includes staining to evaluate for new epithelial defects (*Figure 2*). Where available, AS-OCT also represents a promising imaging modality that can be applied to monitor BKPro patients for occult melt (*Figure 3*).

In light of these considerations, full-time bandage contact lens wear in BKPro patients offers manifold utility. The contact lens protects the corneal surface from desiccation and mechanical trauma and resultant inflammatory processes (62), while also addressing refractive errors, comfort, glare, and cosmesis (66). However, full-time contact lens wear becomes itself a variable increasing the risk of particular complications. As noted previously, contact lens wear presents a consideration to the glaucoma surgeon in regards to tube placement, patch graft placement, and conjunctival coverage, where a suboptimal tube or bleb contour or an inadequate contact lens fit can result in erosion and exposure of the tube (53). Lenses must be routinely changed in order to mitigate the risk of infection as well as to eliminate protein deposits. Notably, life-long daily topical antibacterial prophylaxis remains recommended in all BKPro patients with or without full-time contact lens wear.

Unfortunately, not all patients are able to maintain a contact lens due to abnormal ocular surface contour and/or forniceal foreshortening. SJS and OCP in particular represent the pinnacle of aberrant host immunity alongside late-stage mechanical alterations resulting from the underlying disease process, creating a cascade of processes leading to a published higher rate of corneal melting and device extrusion (20,22,27,67). Given the underlying inflammatory etiology, symblepharon repair in these patients may precipitate episodes of inflammation and disease progression (68). Rather, quiescence of the underlying disease process is critical to decrease the risk of corneal melt (69,70). While comprehensive management of autoimmune conditions is beyond the scope of this review, these successes following titration of immunomodulation to mitigate corneal melt highlight the role of ongoing

inflammation in keratolysis and ultimate implant failure. Most BKPro patients are commonly maintained on topical corticosteroids alone, being one of the advantages of the prosthesis compared to cell-based approaches that require systemic immunosuppression with multiple agents. However, some patients may require oral corticosteroids, topical intravenous immunoglobulin (IVIG), anticollagenase agents such as topical medroxyprogesterone or oral tetracyclines, and systemic immunomodulators (4), the latter in conjunction with a multidisciplinary team including rheumatology and dermatology colleagues where indicated and practical. The inflammatory state of BKPro candidates should be optimized prior to proceeding with implantation. In response to episodes of donor tissue decompensation, infectious processes must be promptly ruled out in order to safely allow for potentially aggressive initial increases in topical and systemic immunotherapy, with close clinical follow-up in order to monitor any progression of melt and superimposed complications in the acutely vulnerable eye.

Ongoing advances also show promise for improving implantation success rates. Improvements in the materials design of the PMMA optic stem surface may increase biointegration between the donor corneal button and the optic stem, decreasing rates of melt and associated complications. Investigations into improving the durability of the donor corneal button using pre-implant collagen-crosslinking are also underway (4).

Infection

Despite the success enjoyed by a growing number of BKPro patients, one of the most meaningful differences originated by transitioning from allograft transplants to a keratoprosthesis is the creation of a lifelong risk of vision- and globe-threatening infection. The design of the prosthesis is such that it remains simultaneously in contact with the microbial traffic of the ocular surface and with the sterile interior of the globe. The material of the prosthetic's central stem does not truly biointegrate with the donor corneal button, where the interface is a potential space that represents a perpetual infection risk. Endophthalmitis is perhaps the most feared complication of BKPro due to its potential devastating outcomes. Incidence is reduced with the use of antimicrobial prophylaxis but can still occur even years after device implantation ranging between 2.9–15% (71-74).

Moreover, as discussed previously, continuous contact lens wear increases the risk of infectious keratitis. In addition, an aberrantly inflamed ocular surface and chronic steroid use may create an environment vulnerable to superimposed microbial infection. This phenomenon is showcased by the higher rates of infectious keratitis and endophthalmitis in BKPro patients with autoimmune disease or a history of chemical injury (71-73). Multiple studies have reported a high rate of keratolysis following infectious keratitis, which can occur during the active infection or following ostensible resolution of the infection (32,75).

Given the lifelong risk of infection, daily prophylactic antibiotics are standard of care for patients with BKPro implants. Preferred regimens vary by surgeon, patient financial considerations, and region, but may include 0.1% polymixin B/trimethoprim or a fluoroquinolone with 1.4% vancomycin or 1% chloramphenicol, where vancomycin may be preferred in patients with severe ocular surface disease (10). Fungal colonization and infection have been reported (76). However, the rate of fungal infection remains overall rare, so there is no consensus on routine anti-fungal prophylaxis and is mostly suggested for high-risk areas. Strategies include periodic sterilization of the ocular surface with 2.5–5% povidone-iodine at regular intervals, e.g., during clinic visits, or intermittent pulses of topical antifungal prophylaxis. A suggested regimen from MEEI consists of natamycin 5% or compounded amphotericin B 0.15% twice daily for a week-long pulse every 2–3 months (10). Regular disinfection or exchange of the bandage contact lens is recommended.

Discussion

Since the BKPro has entered clinical use, our understanding of the pathophysiology of the BKPro eye has improved, allowing us to increase the rates of durable implant retention and visual rehabilitation. Consequently, BKPro implantation has evolved into a viable option for a broad range of patients with corneal blindness and allowed many of its recipient patients to realize the hope of regaining functional vision despite a history of devastating ocular disease. However, given the complexity of these patients and the persistent risks of blinding complications, there remain many challenges ahead of keratoprosthetics surgeons and their patients. Successful KPro implantation is a multi-step, longitudinal process requiring careful, interdisciplinary patient evaluation and selection, involved surgical planning, and dedicated post-operative care.

Improving rates of successful implantation begins with careful identification of patient candidates, both in their clinical attributes and their broader ability

to maintain the intensive follow-up and maintenance required for KPro implant retention. The patient must be thoroughly optimized, with control of ocular surface disease and immune activity, glaucoma status, and anatomic modification where appropriate. This control must ideally be maintained during and following implantation, with particular care undertaken to monitor for evidence of infection, keratolysis, or glaucomatous damage.

Conclusions

Dedicated research initiatives are focused on mitigating the potential risks associated with postoperative complications, thereby enhancing long-term outcomes. A key area of interest is the reduction of RPM formation, a factor that, if successfully addressed, could lead to a diminished occurrence of postoperative angle closure glaucoma, corneal melt, and retinal detachment. Anticipating breakthroughs in glaucoma monitoring technology and advancements in prosthesis design, we are poised to witness a transformative impact on reducing the vulnerability of implanted eyes.

The quest for the ideal artificial cornea is marked by the imperative need for seamless biointegration with host tissue. This integration not only aims to lower the risk of infectious endophthalmitis but also seeks to elevate the retention rate of the device. Despite longstanding challenges in the KPro field, there is optimism surrounding ongoing investigations into devices that seek to enhance the design beyond the limitations of the BKPro model.

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