

Fungal Colonization and Infection in Boston Keratoprosthesis

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Purpose: To determine the incidence of and risk factors for fungal keratitis and endophthalmitis in patients with a Boston keratoprosthesis (KPro) and to determine whether surveillance cultures were helpful in predicting fungal infection.

Methods: A retrospective chart review was performed of 182 patients (202 eyes) who received a type 1 (through cornea) or type 2 (through cornea and lid) KPro between March 1, 1990, and December 31, 2004, and who were followed for at least 1 month (range, 1 month to 13 years; mean, 2.84 years). There were 148 eyes with type 1 and 54 eyes with type 2. Beginning in late 1999, many eyes were given a prophylactic topical regimen containing vancomycin, and many eyes with type 1 KPro were given therapeutic contact lenses. Cases of fungal keratitis or endophthalmitis were analyzed. To determine the fungal colonization rate, 70 surveillance cultures of the ocular or lid surface around the KPro optic were obtained of 36 uninfected KPro eyes (35 patients) at random time-points over 1 year (August 2002 to July 2003).

Results: There were 4 definite and 1 probable fungal infections in 6893 patient-months of follow-up, or 0.009 fungal infections per patient-year. These included 3 cases of definite or probable *Candida* endophthalmitis (*C. parapsilosis*, *C. glabrata*, and *C. albicans*) and 2 cases of mold keratitis (*Alternaria*, *Fusarium*). The rate was higher in eyes receiving a vancomycin-containing topical prophylactic regimen than those with on a non-vancomycin regimen (5 cases/2774 person-months vs. 0 cases/4119 person-months; $P = 0.011$). In eyes with type 1 KPro, the rate was higher with therapeutic contact lens wear than without (4/1682 vs. 0/3115 person-months; $P = 0.015$). Surveillance cultures did not predict fungal infection, and none of the 6 surveillance eyes colonized with fungi (all *Candida*) developed a fungal infection. The prevalence of fungal colonization in KPro eyes had not changed since our 1996 surveillance study (11% vs. 10%, $P > 0.05$).

Conclusion: Fungal infections in KPro eyes have appeared since we introduced broad-spectrum antibiotic prophylaxis and therapeutic contact lenses 5 years ago, but the infection rate remains very low in our mostly New England-based patient population. Cleaning or replacing the contact lens on a regular basis and prescribing a short

course of topical amphotericin at the first visible signs of fungal colonization may prevent these infections.

Key Words: keratoprosthesis, endophthalmitis, fungal colonization, vancomycin, *Candida*

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Keratoprosthesis (KPro) surgery is generally reserved for eyes with advanced disease that have undergone multiple attempts at surgical reconstruction. The serious ocular pathology found in such patients leads to an increased risk of glaucoma,¹ tissue melt with aqueous leak,² device extrusion, chronic inflammation and membrane formation,³ retinal detachment,⁴ macular edema, keratitis, and bacterial endophthalmitis.^{5,6}

Many of the complications associated with Boston KPro devices have been successfully addressed through surgical procedures, design alterations, and medical therapy. There are 2 types of Boston KPro (Fig. 1). The type 1 KPro is used in patients who have retained relatively normal lid function and the ability to maintain a “wet” ocular surface. The type 2 KPro, with its optic extending through a surgically closed lid, is less commonly used and reserved for those with end-stage dry eye conditions.⁷ The problem of ocular surface dehydration has been successfully addressed by the use, since mid-1999, of therapeutic soft contact lenses in eyes with a type 1 KPro.⁸ This lens stays in place for weeks to months and is replaced only when it is lost, dislocated, or shows evidence of accumulation of debris. Bacterial endophthalmitis was a significant problem in the 1990s, especially in eyes with ocular cicatricial pemphigoid (OCP) or a history of Stevens–Johnson syndrome (SJS).⁵ During those years, patients received topical antibiotic prophylaxis with commercially available antibiotics (polymixin–trimethoprim, gentamicin, or ofloxacin). Beginning in late 1999, vancomycin was added to the topical prophylactic antibiotic regimen for all high-risk eyes and many eyes in low-risk categories. This addition has nearly eliminated the problem of bacterial endophthalmitis.⁹ Topical corticosteroids are also used in many KPro type 1 eyes to reduce ocular inflammation. To evaluate whether broad-spectrum antibiotics and soft contact lens wear predispose to fungal colonization and infection, we reviewed our data for evidence of fungal infection in KPro eyes since 1990. We also collected 70 surface cultures from 36 uninfected KPro eyes for fungal surveillance during a 12-month period in 2002–2003 and compared this with our surveillance culture data from 1996, as reported previously.⁵

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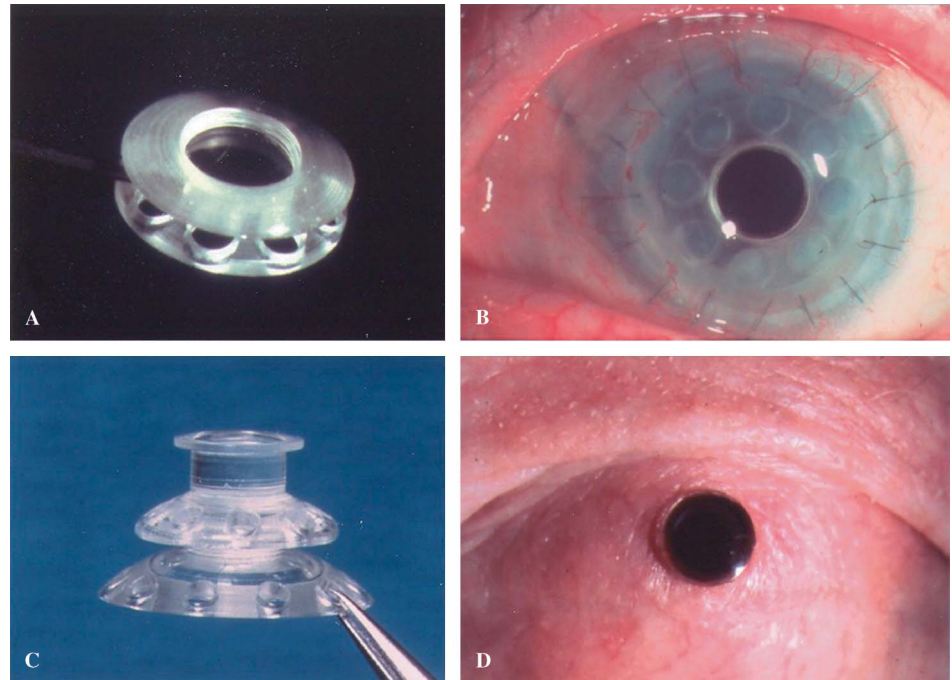


FIGURE 1. Boston KPro. A, Type 1. B, Type 1 in eye. C, Type 2. D, Type 2 in eye.

MATERIALS AND METHODS

Between March 1, 1990, and December 31, 2004, 182 patients received a Boston KPro type 1 or type 2 at the Massachusetts Eye and Ear Infirmary and were followed for at least 1 month postoperatively (range, 1 month to 13 years; mean, 2.84 years). Sixteen patients received a KPro in both eyes (at different times), 3 patients sequentially received both types of KPro in the same eye, and 1 patient received a second KPro of the same type in the same eye, but 8 years after removal of the first KPro. These 20 eyes are counted separately, giving a total of 202 eyes. Eyes receiving an exchange KPro (eg, to repair leaks) were not counted separately.

A KPro was placed in 96 eyes between 1990 and 1999 and 106 eyes from 2000 to 2004. A type 1 KPro was placed in 148 eyes and a type 2 in 54 eyes. The patients had a variety of preoperative diagnoses, which fell into 4 main categories: OCP, SJS, chemical or thermal burns, and “graft failure/other.” This last category included a variety of noncicatizing ocular conditions that led to repeated corneal graft failure, including degenerations, dystrophies, herpes simplex, aniridia, and trauma.

After mid-1999, most patients with type 1 KPros were given soft contact lenses to wear continuously. The lenses used are Kontur lenses (Kontur Kontakt Lens, Richmond, CA), usually either of 16.0 mm diameter/9.8 mm base curve or 18.0 mm diameter/7.0 mm base curve. Prophylactic topical antibiotic drops were prescribed for all patients beginning in 1990 and were usually given twice daily. In recent years, nearly all patients received topical ofloxacin 0.3%, and beginning late 1999, many patients were given topical vancomycin as well. Vancomycin drops were made up by the pharmacy at a concentration of 1.4% (14 mg/mL) and were kept refrigerated by the patient during use and discarded after

1 week. Prednisolone acetate 1% drops were administered according to need to suppress inflammation. In patients with fungal infections, amphotericin was made up by the pharmacy at 0.15% concentration for topical use and 10 μ g for intravitreal injection.

Cultures

Cultures were performed for both bacteria and fungi in all eyes with evidence of keratitis or endophthalmitis. In patients with keratitis, cultures of the ocular surface were performed (cornea in type 1 KPro eyes, lid skin around the KPro nub in type 2 KPro eyes). In endophthalmitis, cultures of aqueous or vitreous were performed. Samples were cultured for bacteria and fungi by inoculation on various culture media, including blood agar, chocolate agar, thioglycolate, and Sabouraud dextrose agar.

In a subset of 36 eyes (35 patients) with no evidence of infection, fungal surveillance cultures of the ocular surface near the KPro were obtained using calcium alginate swabs and streaked on Sabouraud agar. In patients with a type 1 KPro, cultures were obtained from the junction of the cornea or conjunctiva and the edge of the KPro. In type 2 KPro eyes, cultures were obtained from the junction of the eyelid skin and protruding optic.

Fungal Infection

Charts were reviewed of all patients with possible or definite fungal keratitis or endophthalmitis at any time after receiving a KPro. Definite cases included those with a clinical picture consistent with either fungal keratitis or endophthalmitis and who had a positive fungal culture from either the cornea in keratitis or intraocular fluid or device in endophthalmitis. Possible cases included endophthalmitis cases in

which surface cultures grew fungus but intraocular samples were negative.

Fungal Surveillance

Seventy surveillance cultures of the ocular surface were obtained in 36 eyes (35 patients) with type 1 or 2 KPros, as described above. At random time-points during a 12-month period, August 2002 to July 2003, patients had between 1 and 6 cultures obtained (13 eyes had 1 culture, 17 had 2 cultures, 3 had 3 cultures, and 2 had 6 cultures). The interval between cultures in patients with 2 or more cultures varied from 1 to 8 months. The interval between KPro surgery and initial cultures varied from 2 weeks to 5 years. Eyes had either a type 1 (24 eyes) or type 2 (12 eyes) KPro. Patients had a variety of ocular diagnoses, falling into 4 categories: graft failure/other (20 patients), SJS (7 patients, 8 eyes), burn (5 patients), and OCP (3 patients). No eye had signs of infection, and none received antifungal agents. All eyes were receiving topical ofloxacin prophylaxis at the time cultures were taken, and 29 eyes (81%) were also receiving topical vancomycin prophylaxis. Of the 24 patients with type 1 Kpros, 21 (88%) used topical corticosteroids, and 14 (58%) used a contact lens during the surveillance period (neither was used in type 2 eyes).

Statistics

We calculated the incidence rates of fungal infection by exposure to vancomycin and/or contact lenses as the number of eyes that developed a fungal infection after placement of a KPro divided by the sum of the accumulated months of follow-up for all eyes. The start date of follow-up was the date of surgical placement of the KPro, and the end date was either the most recent clinic visit date, the close of the study (12/31/2004), or the onset of fungal infection, whichever came first. In rare cases, all vision in the KPro eye was lost (eg, from glaucoma) or the KPro was removed, and in these cases, those events served as the end date for follow-up. For each KPro eye, follow-up time was allocated into exposed (eg, time on vancomycin) or unexposed (eg, time not on vancomycin) categories. Because fungal infection was rare, we used an exact test to compare incidence rates according to exposure status. We used eyes rather than persons as the unit of analysis, both because the need to use exact methods precluded adjustment for the correlation between fellow eyes and because we thought that fungal infections were likely to be related to eye-specific factors.

RESULTS

Infections

There were 4 definite and 1 probable fungal infections, for a rate of 5 infections in 6893 patient-months of follow-up, or 0.009 infections per patient-year. The patient with the probable infection had a type 2 KPro and the other 4 patients had type 1 KPro. There were 3 definite or probable yeast infections and 2 mold infections (Table 1). Two patients had culture-positive *Candida* endophthalmitis (*C. glabrata* and *C. parapsilosis*), 1 had culture-negative endophthalmitis suspicious for *Candida albicans*, 1 had *Alternaria* keratitis, and 1 had *Fusarium* keratitis and a positive aqueous culture secondary to extension of the keratitis. All patients had received a new or replacement KPro in 2001 or later, and infections developed from 5 to 24 months postoperatively. All infections occurred between 2002 and 2004. At the time of infection, all patients had been using topical prophylaxis with vancomycin and ofloxacin for at least 5 months (range, 5–30 months), and all 4 patients with type 1 KPro had also used a therapeutic contact lens for at least 5 months (range, 5–24 months).

The 4 patients with definite infections recovered vision better than (3 cases) or equal to (1 case) their vision before KPro placement, although in 3 cases, vision was worse than their KPro vision before the infection. Although a preoperative ocular disease classification of SJS carried the highest risk for bacterial endophthalmitis in the 1990s,⁵ none of the cases of fungal endophthalmitis were in this category. Case reports of the patients with fungal infections follow.

Case 1: *C. glabrata* Endophthalmitis

A 74-year-old man with OCP and best-corrected visual acuity (BCVA) of hand motion received a KPro type 1 with Ahmed shunt OD in September 2001; subsequent BCVA was 20/200 because of a macular scar. The patient was given a soft contact lens and used topical vancomycin, ofloxacin, and corticosteroids. In September 2002, a corneal infiltrate was seen by his local ophthalmologist in Canada, and topical amphotericin was added. The contact lens was removed 1 week later, and cultures (on topical amphotericin) were negative. Decreased vision and eye discomfort developed, and endophthalmitis was diagnosed. Vitrectomy was performed with replacement of the KPro with a corneal graft, plus intravitreal injection of amphotericin and vancomycin. Vitreous cultures

TABLE 1. Fungal Infections in Eyes With KPro Between 1990 and 2004

Patient	Ocular Dx	KPro	Infection	Organism	Months Postoperative	Conditions at Infection		
						Vanco*	CL	PF
1	OCP	1	Endophthalmitis	<i>C. glabrata</i>	12	Yes	Yes	Yes
2	Graft failure	1	Endophthalmitis	<i>C. parapsilosis</i>	24	Yes	Yes	Yes
3	OCP	2	Endophthalmitis†	<i>C. albicans</i>	19	Yes	No	No
4	Graft failure	1	Keratitis	<i>Alternaria</i>	5	Yes	Yes	Yes
5	Graft failure	1	Keratitis, endophthalmitis	<i>Fusarium</i>	16	Yes	Yes	Yes

*Topical vancomycin and ofloxacin were used for antibiotic prophylaxis in all 5 eyes before infection onset.

†Endophthalmitis in this patient was probable only (intraocular cultures were negative).

Vanco, vancomycin; CL, contact lens, used only in type 1 eyes; PF, topical prednisolone acetate 1%, used only in type 1 eyes; OCP, ocular cicatricial pemphigoid.

grew *C. glabrata*; pathology of the removed cornea showed budding yeast. He was treated with oral fluconazole, and subsequent BCVA was hand motion.

Case 2: *C. parapsilosis* Endophthalmitis

A 39-year-old woman had a history of congenital glaucoma, corneal scarring (from prior *Pseudomonas* keratitis), and filamentary keratopathy OD. Filamentary keratopathy had resolved with a soft contact lens, and she had a BCVA of light perception (LP). She received a KPro type 1 and Ahmed shunt in December 2001, and BCVA after surgery was 20/200 to 20/400, possibly limited by amblyopia. A therapeutic contact lens was kept in place, and topical vancomycin, levofloxacin, and corticosteroids were given. In July 2003, the contact lens was removed because of white deposits, which grew abundant *C. parapsilosis*, abundant diphtheroids, and in the meat broth only, a gram-negative rod (*Alcaligenes*) sensitive to levofloxacin. Cultures of the conjunctiva and cornea around the KPro front plate were negative. A new contact lens was placed, and topical amphotericin was added to the standard regimen for 2 months. In December 2003, she presented to her ophthalmologist in Pennsylvania with 1 week of decreasing vision, eye redness, and hypopyon. Vision had decreased from hand motion (HM) to LP, and B-scan showed vitreous debris. The Ahmed shunt was removed, aspirates of aqueous and vitreous were taken, and intravitreal vancomycin, amikacin, and amphotericin were given. A light growth of *C. parapsilosis* was cultured from the shunt. Culture of the collagen sheath over the shunt, aqueous, and vitreous grew a very small amount of *Alcaligenes* (growth in broth only for collagen sheath and aqueous cultures, 1 colony on blood agar plate for vitreous cultures). Oral levofloxacin and fluconazole were given for 1 week; topical amphotericin was added to a chronic regimen of topical moxifloxacin and vancomycin. In February 2004, the patient underwent vitrectomy for hemorrhagic vitreitis and retro Pro membrane peel; no signs of infection were found. In March, she presented with eye pain and decreased vision. A vitreous aspirate was taken, and vancomycin, amikacin, and amphotericin were injected. The aspirate grew 2 colonies of *C. parapsilosis*. Oral fluconazole and topical amphotericin were restarted; the vitreous was clear 10 days later. The patient was maintained on topical amphotericin for 4 months, while long-term oral fluconazole prophylaxis was continued. At follow-up in November 2004, the eye remained clear and BCVA was count fingers at 5 ft.

Case 3: Possible *C. albicans* Endophthalmitis

A 79-year-old woman with OCP, prior corneal graft failure, and BCVA of light perception OD underwent KPro type 2 and Ahmed shunt OD in 1998. Leaking developed, and the KPro was replaced in February 2001, with subsequent BCVA of 20/40, including follow-up in June 2002. In August 2002, the patient presented with 1 week of worsening vision. The eye was soft, Seidel-negative, and visual acuity (VA) count fingers at 1 ft, and B-scan showed choroidal effusions. Culture from around the KPro nub grew moderate *C. albicans*. On examination 6 days later, there was an intraocular white infiltrate behind the KPro, adjacent to the lower stem. Vitrectomy, intravitreal amphotericin, and replacement of

the KPro were performed. Intraocular and KPro cultures were negative, and pathology showed chronic granulomatous reaction but no bacteria or fungi. The patient was treated for probable *Candida* endophthalmitis with oral fluconazole 400 mg daily for 6 weeks and topical amphotericin. Although subsequent surface cultures remained negative, the eye developed a retinal detachment and phthisis over the next 4 months and vision OD was lost.

Case 4: *Alternaria* Keratitis

A 59-year-old man with a history of congenital glaucoma and repeated graft failures OD had a BCVA of count fingers at 2 ft. He underwent KPro type 1 in May 2002 and was subsequently maintained on topical vancomycin, ofloxacin, corticosteroids, and given a soft contact lens. His BCVA fluctuated between 20/200 to 20/400, with 1 measurement of 20/80. In October 2002, he complained of 2 days of decreased vision. There was no pain or redness, but the cornea was uniformly pale and slightly white without a distinct infiltrate. Significant vitreitis obscured any view of the fundus. Cultures were taken of the cornea and vitreous, and vancomycin, amikacin, and amphotericin were injected intravitreally. Vitreous cultures were negative, but cornea cultures grew *Alternaria*. The patient was treated with frequent topical amphotericin drops, and the vitreitis rapidly cleared, with subsequent BCVA of 20/60 to 20/70. Three corneal cultures taken over the next 3 months (on topical amphotericin) were negative.

Case 5: *Fusarium* Keratitis and Endophthalmitis

A 74-year-old woman with a history of herpetic keratitis, repeated graft failures, and BCVA of count fingers at 1 ft OD received a KPro type 1 in July 2003. Postoperatively, she received a soft contact lens and topical vancomycin, ofloxacin, and corticosteroids. Her BCVA improved to 20/40. In November 2004, she developed a corneal infiltrate that was suspicious for fungal keratitis. A corneal culture was obtained and topical amphotericin was added. Because of the presence of intraocular cells, a vitreous aspirate and injection of antibiotics (amphotericin, vancomycin, amikacin) were performed 4 days later. The corneal culture grew abundant *Fusarium* (not further speciated), whereas the vitreous aspirate culture was negative. Because of persistent keratitis despite maximal medical therapy, the KPro was replaced 10 days later. Pathology of the removed cornea showed inflamed stroma with hyphae, and cultures of the contact lens, cornea, KPro, and aqueous grew *Fusarium* species. The eye improved on topical amphotericin and oral antifungal agents (itraconazole and then voriconazole). BCVA 6 weeks later was 20/400 and 6 months later was 20/40.

Risk Factors

Both topical vancomycin use and contact lens use were risk factors for fungal infection (Table 2). There were 5 cases in 2774 person-months of follow-up in those using vancomycin and 0 in 4119 person-months of follow-up in those not using vancomycin (P exact = 0.011). Therapeutic contact lenses could be used only by eyes with type 1 KPro, and in these eyes, contact lens use increased the risk of fungal infection (P exact = 0.015). Patients with type 1 KPro using both a contact lens and vancomycin eyedrops were more likely

TABLE 2. Risk Factors for Fungal Infection in KPro Patients

Risk Factor	No. Infections	Person-Months Follow-Up	Incidence*	P
Vancomycin				
Yes	5	2774	0.0018	0.011
No	0	4119	0	
Contact lens				
Yes	4	1682	0.0024	0.015
No	0	3115	0	
Vancomycin + contact lens†				
Both	4	1061	0.0038	0.009
Neither	0	2360	0	

*Incidence is defined as number of fungal infections per person-months of follow-up.

†This study could not separate the relative contributions of these 2 risk factors, because both vancomycin and contact lenses were commonly used together.

to develop a fungal infection than those using neither (P exact = 0.009). However, there was no apparent increased risk in those using both contact lenses and vancomycin compared with either vancomycin use alone (442 person-months, P exact = 0.25) or contact lens wear alone (398 person-months, P exact = 0.28). Because vancomycin and contact lenses were often used together in the same eye, this study could not determine which risk factor was the more important one.

Surveillance

There were 70 surveillance fungal cultures performed over 1 year on 36 uninfected eyes in 35 patients. Twenty-nine patients had negative cultures only. Six patients (6 eyes) had 1 positive fungal culture each (17% of 36 eyes, 8.6% of 70 cultures), as shown in Table 3. Three of these 6 eyes had KPro type 1, but only 2 used a contact lens and topical corticosteroids. The presence or absence of fungal colonization on the first culture did not seem to predict subsequent cultures, as colonization changed over time. In 4 of the eyes with positive cultures, more than 1 culture was taken during the surveillance year, and the other cultures were negative. Negative cultures preceded or followed the positive culture. In 2 patients, both with SJS, 6 cultures were taken over a 10-month period. In 1, the positive culture was followed by 5 negative ones, and in the other, the positive culture was preceded and followed by

TABLE 3. Fungal Colonization in Uninfected Kpro Eyes

Patient	Ocular Dx	KPro	Organism	Follow-Up With No Infection (mo)
1	SJS	2	<i>C. parapsilosis</i>	27
2	SJS	1	<i>C. albicans</i>	26
3	SJS	1	<i>C. albicans</i>	26
4	SJS	2	<i>C. parapsilosis</i>	25
5	graft failure	1	<i>C. parapsilosis</i>	24
6	burn	2	<i>C. parapsilosis</i>	20

Results of surveillance cultures on 6 of 36 eyes during a 12-month period: Aug. 2002 to July 2003.

negative cultures. All positive fungal cultures grew yeast (*Candida* spp.); none grew a mold. Although 4 of the positive cultures occurred in patients with SJS, 3 of these patients had 2 or more cultures. Because yeast colonization seems to fluctuate spontaneously, the chance of obtaining a positive culture from a given eye may increase as more cultures are obtained in that eye over time. If only the first culture result were used for all 36 eyes, only 4 eyes (11%) would have been found to have a positive culture. Compared with the rate of fungal colonization in a surveillance study of performed in 1996,⁵ there was no significant difference (3 of 30, or 10%, vs. 4 of 36, or 11%, $P > 0.05$).

None of the patients in the surveillance group, including the 6 with positive cultures, developed a fungal infection as of December 31, 2004 (19-30 months of follow-up).

DISCUSSION

Topical antibiotic prophylaxis has been necessary to prevent bacterial endophthalmitis in patients with the Boston KPro. Because of troubling results in an earlier study,⁵ vancomycin was added to the topical prophylactic regimen for many patients beginning in late 1999. This addition reduced the overall incidence of acute bacterial endophthalmitis from 12% to 0% and from 39% to 0% in the subgroup of eyes with SJS.⁹ Another intervention, the use of therapeutic soft contact lenses, was introduced mid-1999 and has been of great benefit to patients with ocular surface disease and type 1 KPro. Many patients with type 1 KPro also receive topical corticosteroids, but this treatment has been standard since 1990.

Broad-spectrum antibiotics, corticosteroids, and warm, moist environments are conditions that predispose to fungal infections. This review of the Boston KPro experience may reflect this. Although the overall rate of fungal infection in our KPro patients was low at 0.009 infections per patient-year of follow-up, both vancomycin use and contact lens use increased the risk of infection to 0.02 and 0.03 infections per patient-year, respectively.

Yeast infections were slightly more common than mold infections in our patients (3 vs. 2, respectively), but no species of yeast or mold predominated. When both infection and colonization were considered, *C. parapsilosis* predominated. This was the yeast in 1 case of infection and in two thirds of the cases of fungal colonization in the surveillance portion of this study. The case of infection was preceded by visible colonization 6 months earlier and was characterized by recurrent infections over several months until chronic suppressive antifungal therapy was instituted. This pattern, and the predominance of *C. parapsilosis* found in the surveillance group, may reflect both the increasing prevalence of this non-*albicans* species and its propensity to adhere to plastic devices. *C. parapsilosis* has become an increasingly common species of *Candida* over the past decade and is now the predominant cause of candidemia in some centers.¹⁰ Recent studies show that it also may be the predominate species of *Candida* colonizing the skin of healthy individuals and may be isolated in 30% of hand cultures.¹¹ The species' marked ability to adhere to prosthetic materials has been well documented and is probably related to slime production.^{12,13} There is genetic

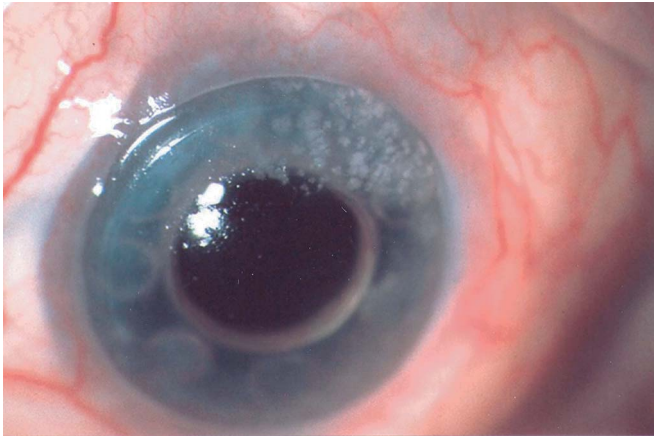


FIGURE 2. “Mulberry-like” *Candida* deposits on soft contact lens.

variation between strains of *C. parapsilosis*, and some strains show greater adherence properties, slime production, and virulence than others.¹⁴ It is possible that the difference between transient colonization versus infection in our patient population was related to this variation.

Can fungal infections be predicted by obtaining periodic surveillance cultures of the peri-KPro ocular surface in uninfected eyes? Unfortunately, our surveillance study of a cohort of 36 eyes does not support this. First, our data suggest that fungal colonization fluctuates spontaneously over time, as has been noted by others.¹⁵ In 4 patients, one positive culture was preceded or followed by negative cultures, although no patient received antifungal treatment. Second, a positive culture was not predictive of subsequent infection in our study. None of the 6 patients with a positive culture developed a fungal infection in the intervening 1.5 to 2.5 years. At present, we do not recommend antifungal treatment of KPro eyes in which there is no evidence of infection or visible fungal colonization. If there is visible fungal colonization on the KPro surface or contact lens, however, we do recommend aggressive medical management to prevent subsequent infection. Heavy colonization may appear as tiny, white, mulberry-shaped precipitates on the surface (Fig. 2). If these are present, we recommend obtaining cultures of the contact lens and KPro, cleaning the KPro surface and removing the contact lens (replacing it with a new lens if necessary), and prescribing a course of topical amphotericin (eg, 4 times daily for several weeks). Evidence of a fungal keratitis may sometimes be seen close to the stem of the KPro (Fig. 3); this may extend to a more profound fungal endophthalmitis. In such cases, a detailed slit lamp examination may reveal the need for vitreous cultures in addition to corneal scrapings; results of the Grams’ stain and cultures will direct the use of topical and/or intravitreal antifungal agents.

The rate of fungal colonization in KPro eyes is approximately 10% and is not significantly higher than is was in our 1996 surveillance study, before we began to use topical vancomycin and therapeutic contact lenses.⁵ In both of these studies, the colonizing fungi were *Candida*. This rate is similar to studies of normal conjunctival flora. Fungi are part of the normal conjunctival flora,^{16–18} with colonization rates

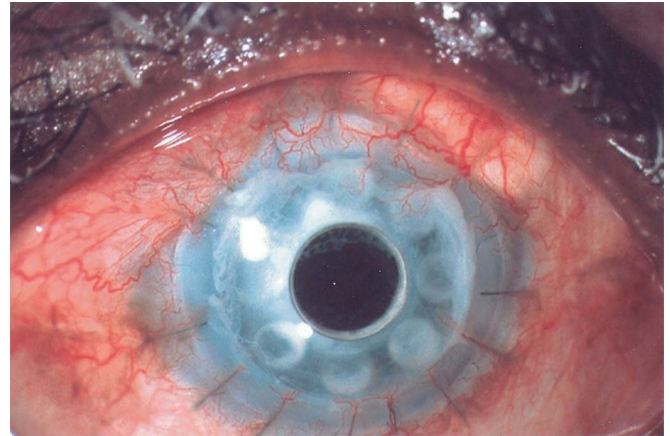


FIGURE 3. Beginning fungal keratitis (case 1). A diffuse white infiltrate with fuzzy borders, starting in cornea adjacent to the stem.

varying from 5% to 25% when tested by routine culture methods. These rates are higher when tested by molecular diagnostic methods such as polymerase chain reaction.^{19,20} Rates of fungal colonization are also higher in tropical regions than in colder areas, and the type of fungi differs. In temperate parts of the United States (eg, New England), yeasts (*Candida*) predominate, whereas in warmer climates in India²¹ or China,²² molds predominate. Molds are a major cause of keratitis and endophthalmitis in tropical countries, and it is possible that topical amphotericin prophylaxis may be important if KPro is used in these countries.

How do we prevent fungal infection in KPro eyes? Topical vancomycin has been dramatically effective in preventing acute bacterial endophthalmitis in these patients, and we cannot eliminate this or a similar gram-positive agent in the prophylactic regimen. Similarly, therapeutic contact lenses have been essential in protecting the ocular surface in many patients with type 1 KPro, and we do not believe that these should be eliminated either. Adding chronic topical amphotericin prophylaxis for all KPro patients does not seem justified, given our low rate of fungal infection. However, an intervention that may have merit is to disinfect or to replace therapeutic contact lenses monthly, rather than leaving them in the eye continuously for many months. Continuous-wear therapeutic contact lenses are associated with a high rate of fungal colonization (27% in 1 study²³). Therefore, disinfecting or replacing the contact lens used in a KPro eye at frequent intervals should reduce the biofilm buildup and may decrease the risk of a fungal eye infection.

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