SURFACE KERATOPATHY AFTER PENETRATING KERATOPLASTY*

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ABSTRACT

Purpose: To determine the type and prevalence of epithelial abnormalities in the intermediate postoperative period after penetrating keratoplasty and to define the donor and recipient variables that influence the status of the graft epithelium.

Design: Prospective cohort study.

Methods: We prospectively followed the clinical course of 80 patients after penetrating keratoplasty. We monitored the status of the corneal epithelium for 3 months after surgery using slit-lamp biomicroscopy and fluorescein staining of the epithelium. Donor characteristics, recipient preoperative and postoperative variables, and postoperative medications were recorded. Epithelial abnormalities were analyzed against these variables by using univariate and combined statistical models to determine the impact of each variable on postoperative epithelial pathology. Main outcome measures included punctate keratopathy, macro-epithelial defects, hurricane keratopathy, rim defects, and filamentary keratopathy.

Results: Sixty-three percent of all patient visits demonstrated punctate epithelial keratopathy (PEK). Hurricane keratopathy (51%) and filamentary keratopathy (14%) constituted the next most commonly observed abnormalities. Older recipient age and the use of topical antibiotics were associated with a higher prevalence of punctate epithelial keratopathy. The odds ratio (OR) for a 1-year increase in age is 1.0276 (95% CI, 1.1013-1.0442), and the OR for using topical antibiotics is 6.9028 (95% CI, 3.1506-15.1239). Use of topical ofloxacin and increased time after surgery were associated with lower prevalence of punctate keratopathy; ORs were 0.9806 (95% CI, 0.9736-0.9876) and 0.3662 (95% CI, 0.1688-0.7943), respectively. Decreased corneal sensation and the presence of anterior blepharitis preoperatively were associated with an increase in hurricane keratopathy; ORs were 8.8265 (CI, 2.3837-32.6835) and 3.2815 (CI , 1.7388-6.1931), respectively. Total storage time for the donor material was also associated with an increased prevalence of hurricane keratopathy (OR, 1.0316; CI, 1.0052-1.0220). Patients with rim defects and macro-epithelial defects were more likely to have antibiotic and topical lubrication prescribed. No specific variable was found to have a significant association with filamentary keratopathy, except possibly for death-to-preservation time, which had a *P* value of .0587.

Conclusions: Surface keratopathy is one of the most common complications of keratoplasty. Our study demonstrates that older age, preoperative lid disease, and decreased preoperative corneal sensation appear to increase the probability of clinically significant epithelial surface abnormalities after keratoplasty. Recognition of these risk factors in advance of surgery will alert the surgeon to the need for appropriate management.

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INTRODUCTION

Penetrating keratoplasty is the most common transplant procedure performed in North America.[1,2] A variety of factors affect graft survival and the visual rehabilitation of the corneal transplant recipient. Although endothelial rejection, infection, and disabling astigmatism are commonly considered the primary causes of physiologic or functional graft failure,[3,4] corneal surface disease can cause significant morbidity and delay in visual rehabilitation. Surface dysfunction may result in a poor refractive surface and can, in addition, cause significant discomfort to patients. Persistent macro-epithelial defects may predispose the graft to infectious keratitis and secondary failure. It is estimated that as many as 25% of grafts may fail on account of surface problems.[5]

In the first several weeks after corneal transplantation, the surface of a corneal graft undergoes enormous

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changes, which frequently include total replacement of the donor epithelium by the recipient. The precise time for complete replacement of the donor epithelium is not known. However, studies of epithelial rejection[4] and sex chromatin in rabbits[6] have indicated that donor epithelium may persist for as long as 1 year after transplantation. Even after epithelial repair by mitosis, migration, and transformation of the host stem cell population, firm adhesion of the newly reconstituted epithelium to the underlying tissue requires production of new basal lamina and proper hemidesmosomal attachment. In a native cornea, this process requires several weeks.[7] In the transplant patient, this process is yet more complicated, since in the early postoperative period, there are the additional insults of the relative denervation of the cornea, poor lubrication, the instillation of frequent and often toxic topical medications, and an abnormal lid-cornea anatomical relationship.

Punctate erosions and vortex keratopathy, along with other types of epithelial abnormalities, are common after keratoplasty, especially in the early postoperative period.[8,9] If not appropriately managed, these ubiquitous problems can escalate into conditions that may threaten the health of the transplant. The critical period for stabilization of most surface problems is in the first 3 months.

In this study, we attempted to determine the prevalence and types of surface disease in the early and intermediate postoperative period as well as to study those donor and recipient factors that might influence the graft surface postoperatively. We followed a cohort of 80 patients prospectively after penetrating keratoplasty, and we systematically observed the status of the ocular surface for 3 months after surgery.

METHODS

Between January 1998 and January 2000, a total of 121 patients were enrolled in this study, with the final analysis including 80 of the original 121 patients enrolled. We obtained an exemption from the Institutional Review Board at the University of California, Davis, since there was no alteration in the treatment regimen of patients whose data were included in this study. All patients underwent penetrating keratoplasty in the Cornea Service, Department of Ophthalmology, University of California, Davis. Surgeries were performed by one of the two faculty corneal surgeons (M.J.M., I.R.S.) or one of two cornea fellows under direct faculty supervision. The mean age of the patients enrolled in this study was 62.05 years (range, 13 to 88) The most common indications for penetrating keratoplasty were Fuchs' dystrophy (28.75%), aphakic or pseudophakic bullous keratopathy (15%), keratoconus (10%), herpes simplex virus (HSV) keratitis (8.75%), and other indications (37.5%). The earliest recorded observation of the epithelium was at 4 days and the longest at 139 days postoperatively.

At initial examination, all patients underwent a complete anterior segment evaluation. This included notation of the status of the lids and lashes, Schirmer test I or basic tear secretion test, and corneal sensation. A Schirmer test value greater than 5 mm of tear advancement on a filter paper strip with anesthesia or 10 mm of tear advancement without anesthesia was considered normal. Corneal sensation was measured by using a Luneau (Cochet-Bonnet) esthesiometer. With this system, corneal sensation was graded from 0/6 (no corneal sensation) to 6/6 (full corneal sensation).

Data on the donor cornea were obtained from the eye bank of origin. These included the age and sex of the donor, death-to-preservation time (hours), preservation-to-surgery time (hours), and the eye bank evaluation of the epithelial status of the donor. Donor epithelial status was recorded as either good (minimal epithelial defect), mild (epithelial defect less than one-third area of the graft), moderate (epithelial defect less than two-thirds area), or severe (epithelial defect more than two-thirds area). Donor corneas were supplied as corneal-scleral buttons in Optisol medium.

SURGICAL PROCEDURE

The host bed was prepared by making a deep partial-thickness trephination using either a disposable Weck™handheld trephine mounted on an obturator or a suction trephination device (the Barron™ radial vacuum trephine or the Hanna-Moria™ trephine). The anterior chamber was then entered with a sharp blade, and the host button was removed using corneal scissors. The donor button was prepared by punching from endothelial surface against a Teflon block with a disposable Weck™ trephine mounted on an Iowa punch. The donor cornea was generally 0.25 or 0.5 mm larger than the recipient bed. The donor cornea was sutured to the host with 10-0 nylon suture either as 16 interrupted sutures or a combination of 12 interrupted and a single running suture, depending on the degree of vascularization of the recipient bed. Donor epithelium was not purposely removed. At the conclusion of each procedure, all patients received a subconjunctival injection of dexamethasone and either cefazolin or gentamicin. All eyes were patched and shielded overnight.

After removal of the patch on the morning after surgery, therapy was begun with ofloxacin drops, 4 times daily, and either prednisolone acetate 1% (Pred-Forte™) or prednisolone sodium phosphate 1% (Inflamase Forte™), 4 times daily. If a large epithelial defect (greater than one-third area of the graft) was present, therapy with

a lubricant ointment such as Refresh PM™ or erythromycin ointment at night was also started. After postoperative day 1, the status of the epithelium, the patient's topical medications, and dosage regimen were recorded for a minimum of 3 separate visits during a period of at least 10 weeks. At each visit, the corneal surface was carefully examined before and after application of fluorescein stain. Punctate keratitis was graded as 0-4, depending on the severity of staining, with 0 being minimal to no punctate staining and 4 being confluent punctate staining covering the entire graft surface. Punctate epithelial keratitis (PEK)–alternatively, punctate epithelial erosion (PEE)–was defined as localized or diffuse punctate microepithelial defects on the surface of the graft. Other epithelial irregularities, including hurricane (vortex) keratopathy, rim epithelial defects, filamentary keratitis, and macro-epithelial defects (>1 mm), if present, were recorded at each visit. Any postoperative complication such as wound leak, infectious keratitis, nonhealing epithelial defects, and graft rejection were recorded. Intraocular pressure was measured at each visit using a Tonopen™, and if pressure was elevated (>22 mm Hg), medical management was initiated.

Patients were excluded from the study for any of the following reasons: incomplete follow-up data (fewer than 3 postoperative visits or an observation period of fewer than 10 weeks), postoperative complications such as infectious keratitis, wound leak requiring the application of a contact lens, or lack of sufficient donor data. The total number of patients meeting the study criteria was 80, with a total of 332 documented visits.

STATISTICAL METHODS AND DATA ANALYSIS

Sixty-seven patients (269 visits) demonstrated differing degrees (0-4) of PEK as the only epithelial abnormality. Only these visits for each patient were analyzed to determine the significance of any associations with punctate keratitis. All 332 visits were used for statistical analysis of other epithelial abnormalities.

For PEK, the statistical analysis of the data was performed as follows: Since the data were longitudinal in nature, in order to determine which variables were significant in the development and severity of PEK, a cumulative logit model was fitted to the data, considering PEK to be the dependent variable. The generalized estimating equation (GEE) method under the GENMOD procedure in SAS PC version 8.0 was used for this model.[10-12] To see the significance of each independent variable, a simple regression model was fitted with each independent variable. These included the preoperative and postoperative factors as already detailed (eg, patient's age and postoperative medications). Variables that were significant ($P \leq .05$) in the isolated simple regression analysis were further included in a multiple regression model to determine their statistical influence on the resulting PEK. Odds ratios were reported on the basis of the final multiple regression model in which the effect of each independent variable on the dependent variable was adjusted by other factors with a P value < .05.

For macro-epithelial defects, rim defects, and hurricane keratopathy, a binary model was used to perform statistical analysis. At each visit, the abnormality was either present or absent. Univariate regression analysis was performed to select significant independent variables. Again, odds ratios were provided only for those variables that remained significant after the influence of other variables were taken into account as dictated by the final multiple regression model.

For filamentary keratopathy, three possible outcomes were recorded. The abnormality was either present or absent; if present, it was either related to or not related to the sutures. Univariate analysis was performed in a similar fashion to select independent variables, and an odds ratio was reported on the basis of the final multiple regression model.

RESULTS

1. ANALYSIS OF RISK FACTORS IN THE DEVELOPMENT OF PEK

The results of the statistical analysis of the factors affecting PEK and its severity are summarized in Tables I through V. The values featured in these tables represent the postoperative data for the 67 patients described who manifested PEK as the only epithelial abnormality. Thirty-four males and 33 females fell into this cohort, totaling 269 visits. In 63% of visits, grade 1 or higher PEK was noted. Ninety-nine visits had grade 0 PEK, 44 had grade 1 PEK, 46 had grade 2, 46 had grade 3, and 34 visits had grade 4 PEK. The variable factors are divided into donor, recipient preoperative, and recipient postoperative.

As shown in Tables I and II, the age of the donor, death-to-preservation time, preservation-to-surgery time, total time, and the epithelial status of the donor all had insignificant impact on development of PEK. The only preoperative factor with a statistical significance in the development of PEK, according to the single variable regression analysis, was the recipient's age, with a P value of .0137 (Table III).

As shown in Table IV, the use of any topical antibiotics with the exception of trimethoprim sulfate had a P value of less than 0.05, indicating a statistically significant effect on PEK using single variable regression. The use of topical

TABLE I: DONOR VARIABLES AND THEIR EFFECT ON PEK

DONOR	MINIMUM	MAXIMUM	MEAN	SD	*P* VALUE
Age (yr)	9	81	57.88	15.06	.9461
Death-to- preservation time (hr)	1	13.25	7.61	3.11	.7125
Preservation-to-surgery time (hr)	5.23	170.83	96.59	45.17	.8439
Total time (hr)	13.38	178	103.22	45.33	.9383

PEK, punctate epithelial keratopathy.

TABLE II: SIGNIFICANCE OF DONOR EPITHELIAL STATUS ON PEK

DONOR	GOOD	MILD	MODERATE	SEVERE	*P* VALUE
Epithelium*	8	41	17	1	.1813

PEK, punctate epithelial keratopathy.
*As detailed in "Methods" section.

TABLE III: SIGNIFICANCE OF RECIPIENT PREOPERATIVE VARIABLE FOR DEVELOPMENT OF PEK

VARIABLE	MINIMUM	MEAN	MAXIMUM	SD	P VALUE
Patient age (yr)	13	62.55	86	17.86	.0137
Patient sex	M 34		F 33		.2045
Preoperative diagnosis	ABK/PBK 11	Fuchs' 21	HSV 6	KCN 7	Other 22	.1476
Corneal sensation	0/6 1	1/6 7	2/6 8	3/6 8	4/6 10	5/6 10	6/6 22	Missing 1	.2392
Schirmer test	Normal 46		Abnormal 21		.9856
Anterior blepharitis	True 17		False 50		.9291
Postblepharitis	True 42		False 15		.1307

ABK, aphakic bullous keratopathy; HSV, herpes simplex virus; KCN, keratoconus; PBK, pseudophakic bullous keratopathy; PEK, punctate epithelial keratopathy.

TABLE IV: POSTOPERATIVE MEDICATIONS AND SIGNIFICANCE ON PEK

TOPICAL MEDICATION	USED	NOT USED	*P* VALUE
Pred-Forte	94	175	.0633
Inflamase	163	108	.1598
Dexamethasone	7	262	.8602
Antibiotic (any)	102	167	
Ocuflox	70	199	<.0001
Erythromycin	19	250	.0036
Polytrim	11	258	.1466
Other antibiotics	16	253	.0054
Lubricant (any)	50	219	.2046
Artificial tears	4	265	.1211
Celluvisc	21	248	.8065
Refresh Plus	16	253	.5318
Other lubricants	3	266	.2449
Other medicine	1	268	.3154

PEK, punctate epithelial keratopathy.

TABLE V: SIGNIFICANCE OF TIME ELAPSED AFTER SURGERY ON PEK

TIME	MINIMUM	MAXIMUM	MEAN	SD	P VALUE
Days	4	139	46.89	35.81	<.0001

PEK, punctate epithelial keratopathy.

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corticosteroids and lubricants did not have a statistically significant effect on PEK.

Time elapsed after penetrating keratoplasty was found to be significant, with a *P* value <.001, as shown in Table V.

Odds Ratio for Factors Significant in the Development of PEK

All variables affecting PEK status with *P* values less than or equal to 0.05 were not finally significant in the development of PEK when adjusted to account for the effect of the other variables. The variables found to have no significant effect on PEK in the combined model were the use of erythromycin ointment and use of "other antibiotics," and the odds ratios for the remaining significant variables are provided in Table VI.

The odds ratios reported in Table VI indicate the relative chance of developing PEK in respect to a given variable. All odds ratios are evaluated relative to 1.000, such that an odds ratio of 1.000 indicates no negative or positive influence on PEK. For example, the odds of having a greater degree of PEK is 0.9806 times less likely at a visit 1 day later (eg, on the 100th postoperative day than on the 99th postoperative day) when all other variables hold the same value. Similarly, the odds of having more PEK and using antibiotics is 6.9028 times that when not using any antibiotics. When individual antibiotics were analyzed, use of Ocuflox was found to show an odds ratio of less than 1.000, indicating lower chance of PEK while using Ocuflox.

2. ANALYSIS OF RISK FACTORS FOR HURRICANE KERATOPATHY

Hurricane keratopathy is a binary variable and was therefore analyzed using all 80 patients with all 332 visits. Hurricane keratopathy was present in 50 visits. Univariate regression analysis of donor, preoperative, and postoperative risk factors yielded the results presented in Tables VII through IX.

Further analysis of the variables with *P* values < .05 in the final model determined that preoperative corneal sensation, anterior blepharitis, and total time elapsed from death of the donor to surgery had an impact on hurricane keratopathy. The odds ratio is shown in Table X.

These numbers indicate that a patient with diminished preoperative corneal sensation is 8.83 times more likely to develop hurricane keratitis than a patient with normal corneal sensation. The other factors can be interpreted the same way.

3. ANALYSIS OF RISK FACTORS FOR MACRO-EPITHELIAL DEFECTS

Presence of a macro-epithelial defect is a binary variable and was analyzed using all 80 patients at all 332 visits. A macro-epithelial defect was detected in 27 of those visits, with 305 visits free of macro-epithelial defects. Univariate regression analysis of donor and of preoperative and postoperative risk factors yielded the results in Tables XI through XIII.

Significant variables in this univariate analysis were the use of prednisolone acetate (Pred-Forte), antibiotics (any), trimethoprim sulfate, and lubricant (any). In the final combined model, only the use of antibiotics (any), trimethoprim sulfate, and lubricant (any) were associated with the development of a macro-epithelial defect. The odds ratios for these variables are provided in Table XIV.

On average, the odds of having macro-epithelial defects and using any antibiotic is 2.7585 times the odds of having macro-epithelial defects and not using any antibiotic, when adjusted for other risk factors in the final

TABLE VI: ODDS RATIO FOR SIGNIFICANT FACTORS AFFECTING PEK

			95% CI	
VARIABLE	ODDS RATIO	SE	MINIMUM	MAXIMUM
Recipient's age	1.0276	0.0084	1.0113	1.0442
Days after surgery	0.9806	0.0036	0.9736	0.9876
Antibiotic (any)	6.9028	2.7624	3.1506	15.1239
Ocuflox	0.3662	0.1447	0.1688	0.7943

PEK, punctate epithelial keratopathy.

TABLE VII: SIGNIFICANCE OF DONOR RISK CHARACTERISTICS FOR THE PRESENCE OF HURRICANE KERATOPATHY

DONOR	*P* VALUE
Age (yr)	.5144
Death to preservation time (hr)	.2642
Preservation to surgery time (hr)	.0404
Total time (hr)	.0389
Epithelial status*	.7827

*As described in "Methods" section.

TABLE VIII: SIGNIFICANCE OF RECIPIENT PREOPERATIVE VARIABLES ON HURRICANE KERATOPATHY

RECIPIENT PREOPERATIVE	*P* VALUE
Patient age	.1093
Patient sex	.7710
Preoperative diagnosis	.0573
Corneal sensation	.0373
Schirmer test	.9600
Anterior blepharitis	.0318
Posterior blepharitis	.0170

multiple regression analysis. The odds of having macro-epithelial defects and using trimethoprim sulfate is 2.3585 times the odds of having macro-epithelial defect and not using trimethoprim sulfate. The odds of having macro-epithelial defects and using a lubricant is 3.9942 times the odds of having macro-epithelial defects and not using any lubricant.

4. ANALYSIS OF RISK FACTORS FOR FILAMENTARY KERATOPATHY

In this study, filamentary keratopathy had 3 possible recordings: none, suture-related, and non–suture-related. We used all 332 visits from 80 patients. Filamentary keratopathy was absent in 285 visits and present in 47 visits. Of these, 9 were felt to be suture-related.

The significance of donor, preoperative, and postoperative risk factors in the development of filamentary keratopathy as determined by a univariate regression analysis is shown in Table XV. No independent variables were found to have statistical significance in relation to the development of filamentary keratopathy after penetrating keratoplasty.

TABLE IX: SIGNIFICANCE OF RECIPIENT POSTOPERATIVE VARIABLES ON HURRICANE KERATOPATHY

RECIPIENT POSTOPERATIVE	*P* VALUE
Time elapsed (days)	.5572
Prednisolone acetate	.3859
Prednisolone sodium phosphate	.1598
Dexamethasone	.3393
Antibiotics (any)	.9118
Ofloxacin	.3015
Erythromycin	.1885
Trimethoprim sulfate	.4180
Other antibiotics	.7713
Lubricants	.3726

5. ANALYSIS OF RISK FACTORS FOR RIM DEFECTS

The presence of rim defect was a binary variable, and all 332 visits by the 80 patients in the study were utilized in this analysis. Patients were found to have no rim defect on 317 visits and rim defect in 15 visits. Table XVI shows the results of the univariate regression analysis of the correlation between the dependent variables studied and the presence of a rim defect.

Although time elapsed since surgery, use of an antibiotic and use of erythromycin were found to be significantly correlated to the presence of a rim defect in the univariate model; only the time elapsed since surgery and the use of erythromycin were correlated with the presence of a rim defect in the final combined model. The odds ratio for the correlation between the presence of a rim defect and these 2 variables is provided in Table XVII.

These results suggest that a longer time elapsed since surgery was associated with a lower prevalence of rim defect. The use of erythromycin was associated with higher prevalence of rim defect.

DISCUSSION

Our study demonstrated that the majority of patients in the first 3 months after penetrating keratoplasty had some degree of punctate keratitis. In 63% of the visits, patients were noted to have grade 1 or higher PEK. Older patient age and use of topical antibiotics were significantly associated with higher probability of PEK. On the other hand, when antibiotics were individually analyzed, use of

TABLE X: ODDS RATIO FOR SIGNIFICANT FACTORS AFFECTING PEK

FACTOR	ODDS RATIO	SE	95% CI MINIMUM	95% CI MAXIMUM
Corneal sensation 0/6 vs 6/6	8.8265	5.8955	2.3837	32.6835
Anterior blepharitis	3.2815	1.0634	1.7388	6.1931
Total time (hr)	1.0136	0.0043	1.0053	1.0220

TABLE XI: SIGNIFICANCE OF DONOR CHARACTERISTICS ON MACRO-EPITHELIAL DEFECT

DONOR	*P* VALUE
Age (yr)	.1589
Death to preservation time (hr)	.6384
Preservation to surgery time (hr)	.1685
Total time (hr)	.1646
Epithelial status*	.5660

*As defined in "Methods" section.

TABLE XII: SIGNIFICANCE OF PATIENT'S PREOPERATIVE CHARACTERISTICS ON MACRO-EPITHELIAL DEFECT

RECIPIENT PREOPERATIVE	*P* VALUE
Patient age (yr)	.8581
Patient sex	.5871
Preoperative diagnosis	.7413
Corneal sensation	*
Schirmer test	.1718
Anterior blepharitis	.1481
Posterior blepharitis	.2415

*Not available with the statistical analysis software used.

TABLE XIII: SIGNIFICANCE OF POSTOPERATIVE VARIABLES ON MACRO-EPITHELIAL DEFECT

RECIPIENT POSTOPERATIVE	*P* VALUE
Days after surgery	.1228
Prednisolone acetate	.0122
Prednisolone sodium phosphate	.1818
Dexamethasone	*
Antibiotic (any)	.0029
Ocuflox	.6433
Erythromycin	.1567
Polytrim	.0352
Other antibiotics	.2805
Lubricant	0.0105

*Not available with the statistical analysis software used.

ofloxacin was associated with a lower probability of PEK. The reason for this is unclear. Our data also indicated that patients tended to have less PEK as time after surgery elapsed. Donor age, time elapsed after harvest, tear function, original diagnosis, and the use of topical corticosteroids did not appear to have a significant effect on PEK. These results correlate well with our previous analysis of PEK after penetrating keratoplasty, in which PEK was the most common surface abnormality postoperatively and was correlated primarily with older recipient age.[13]

The high prevalence of punctate staining after keratoplasty reflects an abnormal epithelial barrier function.[14] Barrier function and stromal fluorescein uptake of the corneal epithelium after keratoplasty have been investigated by other groups.[15,16] Shimazaki and associates[15] studied the barrier function of 69 eyes after keratoplasty by using fluorophotometry. Their study indicated that the barrier function of the epithelial cells was significantly decreased, and stromal fluorescein uptake was increased by a magnitude of tenfold after PKP compared to native corneas. The investigators also noted a direct relationship between recipient age and abnormality in the barrier function of the epithelium. These findings correlate with our observation of increased PEK in older patients. However, these investigators found no relationship between the length of time postoperatively and the barrier function of the epithelium, while we noted that PEK decreased with time after surgery, as might be expected. One explanation for this discrepancy is that in the study by Shimazaki and associates, barrier function was measured with a fluorophotometer and not a slit lamp. Fluorophotometry may be more sensitive in picking up small degrees of dye uptake than slit-lamp examination.

There have been contradictory reports regarding the epithelial barrier after keratoplasty. Boot and colleagues[17] studied epithelial permeability in 27 eyes that had penetrating keratoplasty and found no significant difference between these and normal eyes. In their study, most of the patients (21 of 27 eyes) had keratoconus. Since keratoconus patients tend to be younger, the findings may be attributed to age.

Patients had a higher probability of PEK while receiving any topical antibiotics. Surprisingly, when antibiotics were individually analyzed, patients had a lower probability of developing PEK when taking ofloxacin. Topical antibiotics, especially the aminoglycosides, are known to cause corneal toxicity.[18] To our knowledge, there have been no studies on the effect of ofloxacin on corneal epithelial wound healing. These findings may suggest that ofloxacin is a less toxic antibiotic after keratoplasty. Patel and associates[19] compared the rate of epithelial healing after PRK

TABLE XIV: ODDS RATIO AND CONFIDENCE INTERVALS FOR SIGNIFICANT VARIABLES IN THE PRESENCE OF A MACRO-EPITHELIAL DEFECT

			95% CI	
FACTOR	ODDS RATIO	SE	MINIMUM	MAXIMUM
Antibiotic (any)	2.7585	0.7312	1.6408	4.6376
Polytrim	2.3585	0.5280	1.5209	3.6576
Lubricant (any)	3.9942	1.1651	2.2549	7.0749

TABLE XV: SIGNIFICANCE OF DONOR, PREOPERATIVE, AND POSTOPERATIVE RISK FACTORS IN THE PRESENCE OF FILAMENTARY KERATOPATHY

DONOR	*P* VALUE
Age	.4573
Death-to-preservation time (hr)	.6264
Preservation-to-surgery time (hr)	.4534
Total time (hr)	.3647
Epithelial status*	.7109
Recipient preoperative	
Patient age (yr)	.5852
Patient sex	.1833
Preoperative diagnosis	.3029
Corneal sensation	.8065
Schirmer test	.5391
Anterior blepharitis	.0858
Posterior blepharitis	.6724
Recipient postoperative	
Time elapsed since surgery (days)	.1337
Prednisolone acetate	.4866
Prednisolone sodium phosphate	.7423
Dexamethasone	.4474
Antibiotic (any)	.4060
Ofloxacin	.3673
Erythromycin	.2380
Trimethoprim sulfate	.1340
Other antibiotics	.6811
Lubricant (in general)	.3516
Other medicine	.5162

*As described in "Methods" section.

TABLE XVI: SIGNIFICANCE OF DONOR, PREOPERATIVE, AND POSTOPERATIVE RISK FACTORS IN THE PRESENCE OF A RIM DEFECT

DONOR	*P* VALUE
Age (yr)	.4342
Death-to-preservation time (hr)	.8496
Preservation-to-surgery time (hr)	.1916
Total time (hr)	.2399
Epithelial status *	†
Recipient preoperative	
Patient age (yr)	.9647
Patient sex	.8475
Preoperative diagnosis	†
Corneal sensation	†
Schirmer test	.8702
Anterior blepharitis	.7368
Postblepharitis	.3638
Recipient postoperative	
Time elapsed since surgery (days)	.0206
Prednisolone acetate	.8153
Prednisolone sodium phosphate	.8640
Dexamethasone	†
Antibiotic (in general)	.0069
Ofloxacin	.9586
Erythromycin	.0290
Trimethoprim sulfate	.3294
Other antibiotics	.8488
Lubricant	†
Other medicine	†

*As described in "Methods" section.
†Not available with statistical analysis software used.

when either ciprofloxacin or ofloxacin was used. The investigators noted that patients who were treated with ofloxacin had a statistically significant shorter time to complete re-epithelialization. Whether these observations are applicable to post-PKP corneas is not known.

The prevalence of hurricane keratopathy was 15% of all visits. Decreased preoperative corneal sensation, anterior blepharitis, and total elapsed time from death of the donor to surgical implantation of the cornea were found to be associated with a higher probability of hurricane keratopathy. Our prevalence was lower than that observed by other investigators. Mathers and Lemp[8] noted the prevalence to be as high as 70% after keratoplasty. The follow-up time in their study was longer than ours (up to 18 months), and they also used epithelial specular microscopy to study the configuration of the surface cells, a technique that, again, may be more sensitive than slit-lamp examination. The same researchers indicated that when slit lamp was used, only 30% of patients had a vortex pattern. The application of topical medications may contribute to the development of hurricane keratopathy. Dua and coworkers[20] reported 6 cases of hurricane keratopathy that developed in eyes with no previous ocular surgeries. In 5 cases, long-term topical steroid use was a factor. Mackman and associates[9] also reported 15 cases of hurricane keratopathy after PKP in patients who were using Maxitrol™. We found no association between topical medications and the development of hurricane keratopathy. This may be due to the difference in our postoperative regimens compared to those of other studies. Mathers and Lemp[8] also observed that after suture removal, the vortex pattern resolved.

TABLE XVII: ODDS RATIOS FOR SIGNIFICANT VARIABLES IN THE PRESENCE OF RIM DEFECT

FACTOR	ODDS RATIO	SE	95% CI MINIMUM	95% CI MAXIMUM
Time elapsed since surgery (days)	0.9894	0.0035	0.9825	0.9963
Erythromycin	3.8076	1.5434	1.7204	8.4272

In 8% of the visits, a macro-epithelial defect was reported, and in 4.5% of the visits, a rim defect was recorded. We found the use of any antibiotics, trimethoprim sulfate specifically, and use of lubricants to be associated with higher probability of a macro-epithelial defect. This phenomenon may not, of course, be specific to these substances. Time elapsed from surgery was associated with lower probability of rim defect, and the use of erythromycin was associated with higher probability of rim defect. This probably represents a selection bias, since patients who were found to have large epithelial defects or rim defects were selectively treated with either aggressive lubrication or erythromycin ointment, and the analysis does not suggest a true causal relationship.

The prevalence of epithelial defects in the patients analyzed here is lower than that reported in literature. Previous studies showed that 76% of eyes after PKP for bullous keratopathy had epithelial defects after surgery.[21] Another study reported that 26% of patients after keratoplasty had epithelial defects greater than 2 mm on the first postoperative day.[22] The primary reason for the lower prevalence in our study is that observation of the epithelium in our study was initiated after the first postoperative week. The prevalence of macro-epithelial defects and rim defects was higher in the original cohort of 121 patients. However, if a patient had a nonhealing epithelial defect requiring a contact bandage lens or tarsorrhaphy, precluding the observation of epithelium, the patient was excluded from the study.

We did not find any association between the use of topical corticosteroids and epithelial defects. Corticosteroids have been shown in experimental animals to delay epithelial healing.[23,24] Work by other investigators, however, has not demonstrated a deleterious effect of steroid on the corneal epithelium. Sugar and associates[25] studied 39 eyes after PKP and found no delay in epithelial healing with the use of steroids.

The status of the donor epithelium had no significant effect on the status of the epithelium after surgery. Meyer and Bahn[21] studied the effect of donor epithelium on 66 eyes undergoing keratoplasty and found a direct relationship between the status of the donor epithelium and the length of time that was required for the graft epithelium to heal completely. In their study, the epithelium was checked daily after surgery, and the longest time for complete epithelial healing was 12 days. Our earliest recording was at 4 days postoperatively, and much more commonly it was at 7 days. Therefore, our data may have missed the period of time during which the donor epithelium has the greatest effect. In addition, the corneas in their study were stored in McCarey-Kaufman medium, while all the corneas used in the present study were stored in Optisol™.

Work by Chou and associates[26] and Kim and colleagues[27] demonstrated that longer storage time and longer death-to-harvest time were associated with epithelial defects after keratoplasty. Our data did not show any correlation between storage time and epithelial defect. We did, however, note an increase in the probability of hurricane keratopathy within an increased total time from death to transplantation. It should be noted that in both the studies mentioned, the epithelial defects were recorded 1 day after the transplant, while our observations started later in the postoperative course. It would be expected that most epithelial abnormalities on the first postoperative day would be related to the donor epithelium and not the host.

We noted filamentary keratitis in 14.2% of the visits. None of the variables analyzed in this study appeared to be significant in the development of filamentary keratitis. In a previous report by Rotkis and associates, 39% of patients with the preoperative diagnosis of keratoconus had postoperative filamentary keratopathy. However, when the investigators analyzed their data, no statistically significant relationship between the preoperative diagnosis and the development of filamentary keratitis was found.

We recognize that there may be concerns about methodology that must be considered before drawing firm conclusions from this data. First, at least 4 different surgeons participated in the surgery. Although our analysis did not suggest that surgeon differences were associated with the prevalence of postoperative surface changes, difference in surgical technique could potentially play a role in the type and prevalence of surface changes in the postoperative period. In this study, the 2 primary surgeons (M.J.M., I.R.S.) used similar surgical techniques and postoperative treatment regimens. All surgeries were under their direct supervision both intraoperatively and postoperatively. We felt that this controlled adequately for surgeon differences. In addition, the estimates of severity of postoperative surface changes were graded in a subjective fashion by different observers in the postoperative period. To control for subjective differences, the observers used "reference diagrams" that were included on each postoperative evaluation sheet, allowing the observer to "grade" by comparison to the reference drawing. This methodology was employed to standardize as much as possible the estimates of the severity of surface disease during postoperative assessments.

Most ophthalmologists who perform corneal transplantation or care for corneal transplant patients express concern about postoperative complications, including graft rejection and infection. These are, nonetheless, relatively rare, albeit serious complications. However, surface keratopathy is ubiquitous after keratoplasty. While it

may be transient, it can also produce significant adverse symptoms for the patient, may delay visual rehabilitation, and may place the eye at risk for more serious, vision-threatening complications. The purpose of this study was, therefore, to highlight the types and extent of this very commonly encountered postoperative problem. Our study demonstrates that older age, preoperative lid disease, and decreased preoperative corneal sensation appear to increase the probability of clinically significant epithelial surface abnormalities after keratoplasty. While these associations are not unexpected, recognition of these risk factors in advance of surgery will alert the surgeon to the need for appropriate management. This recognition will hasten the visual recovery of the patient and minimize the more serious risks engendered by an incompetent surface after corneal transplantation.

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DISCUSSION

DR WOODFORD S. VANMETER. Mr. President, Mr. Secretary, members and guests: I appreciate the opportunity to discuss this paper. Many thanks to the authors for sending the manuscript to me promptly.

AJ Bron reported in 1973 whorl patterns in the post-graft corneal epithelium.[1] Vortex patterns of the corneal epithelium,[2] and hurricane keratopathy[3] have both been described following keratoplasty. All corneal transplant surgeons are familiar with post-keratoplasty epitheliopathy, which can range from complete absence of the corneal epithelium with basement membrane damage to a perfectly clear and healthy epithelium on day 1 following keratoplasty. Stulting and colleagues showed in 1987 that the absence of the corneal epithelium did not affect graft rejection, but Stulting noted that the overall failure rate in his series was higher in the group with the epithelium off than the group with the epithelium on, underscoring the importance of a healthy epithelium.[4]

Epithelial regeneration on a graft is more complicated than epithelial regeneration in a native cornea. Donor corneal epithelium itself has been stored for days in tissue culture medium, and may not be amenable to instant resurfacing even under ideal conditions. Relative denervation of the cornea, poor lubrication, installation of frequent and often toxic topical medications and an abnormal cornea and lid anatomical relationship all may impede restoration of normal surface.

The authors have set out to determine the type and

prevalence of epithelial abnormalities in the intermediate postoperative period and to define the donor and recipient variables that influence the status of the graft epithelium. Using slit lamp examination and fluorescein staining, the authors examined the donor epithelium and recipient variables such as dry eyes, blepharitis, corneal sensation and postoperative medications. Outcome measures examined were superficial punctate keratitis, epithelial defects, hurricane keratopathy, rim defects and filamentary keratitis measured by slit lamp examination and fluorescein staining. A detailed statistical analysis was provided using univariate and combined statistical models to determine the impact of each variable on postoperative epithelial pathology.

The authors found that 63% of patients had superficial punctate keratitis, which correlated with old age and topical antibiotics administered postoperatively. Fifty-one percent of patients developed hurricane keratopathy, which was associated with decreased corneal sensation, blepharitis and increased storage time.

With any detailed statistical model, clinically significant results depend on carefully controlled variables. I would like to ask the authors to comment on 3 additional features in this study which might help corneal surgeons utilize the conclusions noted. 1) Reliable information on the donor epithelium status is difficult to determine. Not all surgeons perform biomicroscopic evaluation of the donor cornea prior to keratoplasty. The use of lubricating ointment, antibiotics and ice on the cadaver prior to harvesting the cornea is difficult to determine in most circumstances. A wide variety of antibiotics, (including aminoglycosides, neomycin and povidone-iodine), are used in preparation of the donor cornea. Cost controls limit the options of many eye banks and cheaper substitutes to quality antibiotics are constant temptation. 2) The actual mechanism for preservation of the epithelium intraoperatively is not mentioned in this paper, although many surgeons now use viscolastic to help the corneal epithelium. Use of topical Healon instead of balanced salt solution to maintain the corneal epithelium has been advocated.[5] In addition to intraoperative care of the epithelium, surgical time, which would obviously be increased with additional procedures or with residents or fellows involved in the surgery, is important. 3) Finally, the status of the epithelium on day 1 is not noted. The authors used 1 week as the time of the first observation. Corneal epithelial status on day 1 can vary from a complete epithelial defect to a normal epithelium, and this author (WSVM) anecdotally notes that those patients with a completely normal epithelium on day 1 have fewer surface problems than those with large epithelial defects on day 1. Measures which promote a healthier epithelium during and immediately after surgery reduce the likelihood of epitheliopathy in the intermediate post-operative period.

Dr. Mannis and co-workers have previously linked recipient age to the development of surface disease,[6] a variable that can hardly be obviated by the operating surgeon. In that paper, postoperative surface keratopathy was not associated with donor epithelial status, suggesting that intraoperative or postoperative variables are mainly responsible for the changes noted in the postoperative period. However, because preoperative donor assessment is performed by multiple observers, many of whom do not have medical backgrounds, the possibility remains that some preoperative donor epithelial features to go unnoticed, due to the imperfection of undisciplined senses.

The authors should be commended for their thoughtful attention to post-keratoplasty epitheliopathy and for their detailed statistical analysis of possible contributing factors. The relative risk of elderly patients with lid disease, keratoconjunctivitis sicca, or glaucoma medications should be recognized in the preoperative evaluation of the keratoplasty patient. Early recognition and treatment of surface disease, whether by observation, lubrication or tarsorrhaphy, may help reduce the extent and severity of post-keratoplasty epitheliopathy. The authors effectively demonstrate that avoiding postoperative mechanical and chemical trauma to the graft and nurturing the corneal surface can improve graft longevity and reduce the incidence of post-keratoplasty complications.

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[Editor's note] DR LINSEY FERRIS commented that supportive measures such as artificial tears, punctal occlusion, and Healon could produce both beneficial and deleterious effects. He asked about the use of soft contact lenses after keratoplasties; what is the best lens and when should it be used. DR DAN B. JONES asked about the role of postoperative topical drugs such as steroids, antibiotics (which ones, for how long and why?), other topical medicines (especially glaucoma drugs), and artificial tears (were they

routinly used and were they preservative free?), DR KENNETH R. KENYON noted that over 25% of keratoplasties fail because of ocular surface problems. He emphasized the importance of evaluating the status of the corneal epithelium, particularly at the limbus, before surgery to determine if additional preventative measures such as punctal occlusion, tarsorrhaphy, amniotic membrane grafts, or limbal autographs should be used. DR THOMAS O. WOOD mentioned that he had almost eliminated postoperative problems from ocular surface disease by doing a simple tarsorrhaphy with a nylon suture in almost all of his cases and thermal punctal occlusion in many.

DR MARK J. MANNIS. I would like to thank Dr VanMeter for his thoughtful comments on our paper. The attempt to correlate the types and degree of surface disorders with the many variables that factor into the dramatically rearranged corneal surface after keratoplasty is a daunting task. We agree that one must take into account a multiplicity of potential influential factors including pre-operative donor status, the length of surgery and the specific surgical techniques employed, and, of course, the many factors that come into play post-operatively. In the analysis of our results, some of the findings were as we had anticipated. Others were counter-intuitive. The challenge has been to determine which of these factors are true clinical phenomena and which are purely statistical entities.

In answer to the specific areas of concern articulated by Dr VanMeter, we would comment as follows:

First, with regard to the statement that the eye bank evaluation of the donor epithelium is not standard across the board, we agree. The American eye banking system has made tremendous strides in standardizing the tissue evaluation process. Nonetheless, it is just beginning to develop standards of evaluation and description that utilize similiar terminology and that are translateable from city to city and from eye bank to eye bank. In the present study, virtually all tissue was funneled to the surgeons through a single eye bank, upon which we could rely for uniform assessment. It is accurate to say, however, that most corneal surgeons do not personally evaluate donor epithelium prior to the use of the tissue and that they rely on the assessment of the eye bank personnel. Perhaps our results should suggest that in higher risk cases, special effort should be made to ensure that the donor epithelium is healthy and intact and is personally evaluated by the surgeon prior to keratoplasty.

The second issue–that of attempts to preserve the epithelium during the procedure–is also very important. We did not control for these factors in this study. Indeed, in some cases we applied viscoelastic to the surface of the graft during surgery while in others, only standard lubrication with balanced salt solution was employed. These techniques were neither recorded nor isolated as variables in the study. We agree, nonetheless, that the post-operative status of the epithelium may vary significantly depending on factors, including the length of surgery, the degree of hydration, and conscious attempts by the surgeon to avoid epithelial trauma.

Finally, we agree that this study does not specifically address the immediate post-operative status of the graft epithelium. The corneal epithelium on the first post-operative day, as Dr VanMeter has correctly described, may range from being totally intact to being completely absent. While our treatment of the surface may differ clinically based on the findings on post-operative day one, it is not clear that the first post-operative day is truly predictive of the subsequent course long-term. We believe that the status of the recipient's surface is far more important to efficient re-epithelialization of the graft than is the status of the donor epithelium on day one. An intact epithelium provides a "jump start" for surface maintenance, but it does not determine the subsequent course. The long-term status of the epithelium is largly recipient dependent. We plan to return to our database to evaluate this issue in the near future.

Dr Dan Jones has aptly commented on the nature of the medications used in this series, specifically with regard to the use of the solutions versus suspensions. Contrary to our expectations, we did not correlate increased or more severe surface keratopathy with suspensions.

We would also concur with Drs Linsey Farris and Thomas Wood that the surgeon can vastly improve the surface rehabilitation of the patient by employing adjunct measures including temporary or permanent punctal occlusion, temporary tarsorrhaphy, as well as the judicious use of therapeutic contact lenses.

In summary, we have attempted to identify those individuals who would be at significant risk for surface problems after keratoplasty. The complexity of the issues makes this a difficult task. Nonetheless, in the elderly patient or the patient with dry eye, blepharitis, or mechanical lid problems that can be identified in advance of surgery, special measures to nurture health of the surface can be undertaken before, during and after the procedure. We thank Dr VanMeter again for his comments, and we appreciate the opportunity to present these data before the American Ophthalmological Society.