Fungal Infection After Descemet Membrane Endothelial Keratoplasty: Incidence and Outcomes

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Purpose: The aim of the study was to describe the incidence, presentation, management, and outcomes of fungal infection after Descemet membrane endothelial keratoplasty (DMEK).

Methods: Retrospective case series of culture-proven fungal infections after DMEK reported in the literature, directly by surgeons, and to the Eye Bank Association of America from January 1, 2011, to December 31, 2020.

Results: The domestic incidence of fungal infections, fungal keratitis, and fungal endophthalmitis after DMEK from 2011 to 2020 was 3.5, 1.3, and 2.2 per 10,000 cases, respectively, with no significant increasing trend. Thirty-four cases were identified, 14 (41.2%) published and 20 (58.8%) unpublished. Donor tissue fungal cultures were performed in 20 of the 34 (58.8%) cases and were positive in 19 of the 20 (95.0%), all but one *Candida* species. Recipient fungal cultures were performed in 29 of the 34 (85.3%) cases and were positive in 26 of the 29 (89.7%), all but one *Candida* species. Infection presented a mean of 33 ± 38 days (median 23, range 2–200, outlier 949) after transplantation: 25 (73.5%) with endophthalmitis and 9 (26.5%) with keratitis. Topical, intrastromal, intracameral, intravitreal, or systemic antifungal therapy was used in all 27 eyes with treatment data. Surgical intervention (DMEK explantation or partial removal, repeat endothelial keratoplasty, penetrating keratoplasty, and/or pars plana vitrectomy) was required in 21 of the 27 (77.8%) eyes. The corrected distance visual acuity at the last follow-up was ≥20/40 in 13 of the 27 (48.1%) eyes and counting fingers or worse in 6 of the 27 (22.2%) eyes.

Conclusions: Fungal infection is a rare but serious complication of DMEK that results in counting fingers or worse corrected distance visual acuity in nearly a quarter of eyes.

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Since 2012, endothelial keratoplasty (EK) has been the most commonly performed type of corneal transplantation in the United States.[1] However, in parallel with the increasing popularity of EK, there has been growing concern over the increasing rate of postoperative fungal infections. A report from the Eye Bank Association of America (EBAA) described an increasing trend in the incidence of postkeratoplasty fungal infections from 2007 to 2014, mostly associated with EK, with an overall fungal infection rate of 0.041% after EK compared with 0.012% after penetrating keratoplasty.[2,3] Fungal infections after Descemet stripping endothelial keratoplasty (DSEK) are associated with a poor visual prognosis, with final vision better than 20/40 in only approximately a quarter of reported cases,[4] likely due to the sequestration of organisms between the donor and host. Although medical treatments, including topical, oral, intrastromal, and intracameral antifungal therapy, have been used in all reported cases, surgical intervention is required to eradicate infection in most cases, with penetrating keratoplasty being performed in 87.5% (21/24) of reported cases.[4–7]

Although the total number of EK procedures has increased each year since 2010, the number of DSEK procedures each year since 2014 has decreased because of an increase in the annual number of Descemet membrane endothelial keratoplasty (DMEK) procedures performed.[1] Although DMEK procedures accounted for 45% of all EK procedures performed in 2020, there are no reports on the incidence of fungal infection after EK published after 2014, so it remains unknown what effect the domestic shift from DSEK to DMEK has had on the incidence of postoperative fungal infection. A review of the English-language literature reveals only 6 case reports or small series that describe a total of 14 eyes with culture-proven fungal infection after DMEK.[8–13] Similar to the reported management of fungal infection after DSEK, most of these 14 eyes required surgery to eradicate the infection, indicating a limited response to antifungal medical treatment. Unfortunately, the small number of cases, varied treatment strategies, and nonstandardized reporting of treatment outcomes prevent meaningful assessment of the efficacy of the various management strategies in treating fungal infection after DMEK.

We sought to gain a better understanding of the incidence, presentation, management, and outcomes of fungal infection after DMEK through a systematic review of published cases and cases reported to the Eye Bank Association of America Online Adverse Reaction Reporting System. With this information, we can determine the annual and overall incidence of culture-proven fungal infection after DMEK, which is essential to making informed decisions regarding whether strategies to decrease the risk, such as antifungal supplementation of the cornea storage media, are needed. In addition, an analysis of the clinical course of fungal infection after DMEK, including response to various treatment regimens, is essential to developing treatment recommendations for ophthalmologists who currently have no evidence-based guidelines for the treatment of post-DMEK fungal infection.

METHODS

Determination of the Annual Incidence of Fungal Infection After DMEK

A search of the EBAA Online Adverse Reaction Reporting System (OARRS) was performed to identify all cases of keratitis and endophthalmitis in the United States reported after keratoplasty procedures performed between January 1, 2011, and December 31, 2020. The cases were analyzed to identify those that occurred after DMEK and were associated with a positive donor and/or recipient fungal culture, as well as a negative recipient bacterial culture, when performed. The annual and total incidence rates of domestic post-DMEK fungal keratitis, endophthalmitis, and overall infection (keratitis + endophthalmitis) between January 1, 2011, and December 31, 2020, as reported in the EBAA Statistical Report, were then calculated.[1] The Cochrane–Armitage test was used to identify a trend in the incidence of fungal keratitis and endophthalmitis during this period.

Identification of Cases of Fungal Infection After DMEK

This study was conducted in compliance with the Health Insurance Portability and Accountability Act and complied with all tenets of the Declaration of Helsinki. Cases of culture-proven fungal keratitis or endophthalmitis after DMEK surgery were identified from 3 sources: the English-language peer-reviewed literature (using the following search terms in PubMed: Descemet membrane endothelial keratoplasty; DMEK; fungal keratitis; and fungal endophthalmitis), the EBAA OARRS (as described in the previous section), and from several DMEK surgeons who were aware of the authors' interest in identifying cases of fungal infection after DMEK based on presentations and discussions at conferences and contacted the authors regarding additional unpublished cases from their practices.

Data Collection and Analysis of Cases of Fungal Infection After DMEK

For previously published cases, the authors of each publication were contacted to collect the following information: donor demographics and tissue characteristics; donor tissue culture results; recipient demographics; recipient preoperative ocular examination findings; surgical details; time from surgery to onset of infection; recipient culture results; fungal infection presentation; medical and surgical management; clinical course; visual and anatomic outcomes; and data regarding the mate donor cornea characteristics, culture, and recipient outcomes. Management was categorized by medical and surgical interventions. Medical interventions assessed included the antifungal agent(s) used, the route(s) of administration [topical, intrastromal, intracameral, intravitreal, and systemic (oral or intravenous)], frequency, and duration of treatment. Surgical interventions assessed included DMEK graft explantation (removal without replacement of a DMEK graft or performance of another form of keratoplasty at the same time), repeat EK (DMEK or DSEK), penetrating keratoplasty, and pars plana vitrectomy.

For unpublished cases that were not present in the OARRS database, the same information was requested from the surgeon who contacted the authors regarding the case. For cases that were identified in the OARRS database and were determined to not correspond to a previously reported case, most of the aforementioned information was available other than data regarding medical and surgical management, clinical course, and visual and anatomic outcomes. The eye bank that reported each case to the OARRS was contacted and asked to contact the operating surgeon to determine his/her willingness to have the authors contact him/her about the reported adverse event (the identity of the surgeon is not contained in the OARRS database). If the surgeon agreed, the authors contacted him/her to request the treatment and outcome data. In the event of inconsistencies between data collected from different sources regarding the same case, data provided by surgeons to the research team were used, when available, and when not, published data were used.

The primary outcome measure was final corrected distance visual acuity (CDVA), categorized by the percentage of eyes with a final CDVA $\geq$ 20/40, $\geq$20/200, or decreased by $\geq$ 2 lines (Snellen) from preoperative CDVA. Snellen fractions were converted to logMAR values for analyses, with counting fingers, hand motion or light perception, and no light perception considered 1.8, 2.3, and 2.6 logMAR, respectively.[14,15] Secondary outcome measures included the need for surgical intervention and recurrence of infection after treatment. Associations of selected medical and surgical interventions with visual acuity outcomes were evaluated using the Fisher exact test. Statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp, Armonk, NY). *P* values were considered statistically significant if less than 0.05.

RESULTS

Incidence of Fungal Infection After DMEK

During the 10-year period from January 1, 2011, to December 31, 2020, 60,042 DMEK procedures were performed in the United States, with 21 cases of fungal infection after DMEK reported to the EBAA OARRS, for an overall

domestic incidence of 0.00035 (0.035%, 3.50 cases per 10,000). Subdividing fungal infections into keratitis (8 cases) and endophthalmitis (13 cases) revealed incidences of 0.00013 (0.013%, 1.33 cases per 10,000) and 0.00022 (0.022%, 2.17 cases per 10,000), respectively (Table 1). The highest annual incidence of fungal infection after DMEK was in 2014 at 0.00070 (0.070%, 6.98 cases per 10,000), with the peak incidences of fungal keratitis in 2014 (0.00035, 0.035%) and fungal endophthalmitis in 2013 (0.00066, 0.066%) (Table 1). The Cochrane–Armitage trend test did not reveal a statistically significant trend in the incidence of fungal infection ($P = 0.61$), fungal keratitis ($P = 0.71$), or fungal endophthalmitis ($P = 0.58$) after DMEK during the period from 2011 through 2020.

DMEK Donor and Recipient Demographic Information

Thirty-four cases of fungal infection (34 eyes) after DMEK were identified: 14 (41.2%) cases from the literature,[8–13] of which 8 (3 domestic and 5 international) had been reported to the OARRS, and 20 (58.8%) unpublished cases, of which 18 (90.0%) had been reported to the OARRS and 2 (10.0%) were surgeon reported (see Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B422). As donor tissues in 3 cases from the literature (28, 29, and 32) were sourced from European eye banks, they were not included in incidence calculations, which were based only on domestic DMEK cases that were reported to the OARRS, but were included in the analysis of presentation, management, and outcomes. The 34 donor corneas were recovered from 31 unique donors, indicating the inclusion of 3 donor pairs in the data set. The mean donor age was 65.7 ± 9.2 (median 67, range 34–86) years, the mean death to preservation time was 13.2 ± 7.2 (median 11.6, range 3–41) hours, and the mean death to surgery time was 7.0 ± 2.8 (median 7.0, range 4–17) days (Table 2). Three of the 34 corneas (8.8%) were stored in amphotericin B, being added to Optisol-GS (case 18) and Dulbecco modified Eagle medium (DMEM, cases 28 and 29). Twenty-one (61.8%) grafts were eye-bank–prepared and 13 (38.2%) were surgeon-prepared. The mean recipient age was 69.0 ± 10.1 (median 70, range 34–86) years, and the most common indication for DMEK surgery was Fuchs endothelial corneal dystrophy (29/34 cases, 85.3%). The preoperative CDVA was ≥20/200 in all 27 eyes (100%) and ≥20/40 in 10 of the 27 (37.0%) eyes for which preoperative visual acuity data were available.

Infection Presentation

Fungal infections presented at a mean of 33 ± 38 days (median 23, range 2–200, outlier 949; missing data: 1) after surgery, predominantly as endophthalmitis (25/34 eyes; 73.5%) and less commonly as keratitis (9/34 eyes; 26.5%) (Fig. 1, Table 3). Although most infections appeared within the first postoperative month (20/33; 60.6%), a third presented between 1 and 3 months after surgery (11/33; 33.3%) and 2 (2/33; 6.1%) presented more than 6 months after surgery (at 6.7 months and 2.6 years; missing data: 1).

Fungal Culture Information

Donor rim fungal cultures were performed for 20 of the 34 (58.8%) cases, with positive results in 19 of the 20 (95.0%) cultures: 18 for *Candida spp* and 1 for unspecified yeast (Table 3). Recipient fungal cultures were performed on corneal tissue, aqueous fluid, and/or vitreous fluid in 29 of the 34 (85.3%) cases. Of these, 26 (89.7%) cultures were positive: 25 for *C. spp* and 1 for *Purpureocillium lilacinum.* Both donor and recipient fungal culture information was available for 11 eyes, with 9 (81.8%) of these pairs positive for *C. spp*, of which 7 (77.8%) showed species concordance.

TABLE 1. Incidence of Fungal Keratitis, Endophthalmitis, and Total Fungal Infections After Descemet Membrane Endothelial Keratoplasty by Year From 2011 to 2020

	Total Fungal Infections (Keratitis + Endophthalmitis)		Fungal Keratitis*		Fungal Endophthalmitis*		
Year	No. Cases	Incidence per 10,000	No. Cases	Incidence per 10,000	No. Cases	Incidence per 10,000	DMEK Procedures†
2011	0	0.00	0	0.00	0	0.00	344
2012	0	0.00	0	0.00	0	0.00	748
2013	1	6.57	0	0.00	1	6.57	1522
2014	2	6.98	1	3.49	1	3.49	2865
2015	0	0.00	0	0.00	0	0.00	4694
2016	2	3.10	2	3.10	0	0.00	6459
2017	5	6.55	2	2.62	3	3.93	7628
2018	2	1.86	1	0.93	1	0.93	10,773
2019	5	3.78	2	1.51	3	2.27	13,215
2020	4	3.41	0	0.00	4	3.41	11,794
Total	21	3.50	8	1.33	13	2.17	60,042

*Based on recipient or donor culture.
†Numbers reflect corneal tissue distributed and used within the United States only.

TABLE 2. Donor and Recipient Demographics of Cases of Fungal Infection After Descemet Membrane Endothelial Keratoplasty

	Donor					Recipient				
Case Number	Age	Cause of Death	Death to Preservation (h)	Death to Surgery (d)	Storage Medium	Sex	Age	Eye	Indication for DMEK	Pre-DMEK CVDA
1	71	Congestive heart failure	11.0	4	Optisol-GS	F	70	OS	FECD	20/20
2	67	Liver failure	24.0	7	Optisol-GS	F	76	OS	FECD	20/30
3	69	Pulmonary fibrosis	14.0	5	Life4C	F	59	OS	FECD	20/30
4	74	Cardiac arrest	10.5	7	Optisol-GS	M	75	OD	FECD	20/40
5	34	Cardiac arrest	10.0	6	Optisol-GS	F	59	OD	Regraft	20/60
6	72	Myocardial infarction	10.5	5	Optisol-GS	F	78	OD	FECD	20/60
7	68	Coronary artery disease	17.0	7	Optisol-GS	—	69	—	FECD	—
8	56	Cardiac arrhythmia	15.0	9	Optisol-GS	M	77	OD	FECD	20/60
9	63	Subarachnoid hemorrhage	5.7	6	Optisol-GS	M	65	OD	Regraft	20/120
10*	66	Cardiomyopathy	13.6	10	Optisol-GS	F	84	OD	FECD	20/120
11	69	Congestive heart failure	8.9	7	Optisol-GS	F	61	OS	FECD	20/50
12**	71	Metastatic carcinoma	15.8	7	Optisol-GS	M	68	—	FECD	20/80
13**	71	Metastatic carcinoma	15.8	7	Optisol-GS	M	72	—	FECD	20/80
14	59	Metastatic uterine leiomyosarcoma	11.2	6	Optisol-GS	M	73	OD	FECD	20/60
15	70	Probable myocardial infarction	23.8	8	Optisol-GS	M	60	OD	Regraft	20/30
16	63	Heart disease	5.0	5	Optisol-GS	—	72	—	FECD	—
17	52	Cardiac arrest	23.9	4	Optisol-GS	—	71	—	FECD	—
18	59	Lung cancer	7.0	6	Optisol-GS†	—	86	—	FECD	—
19***	68	Pancreatic cancer	8.0	6	Optisol-GS	—	74	—	FECD	—
20***	68	Pancreatic cancer	8.0	6	Life4C, Optisol-GS‡	—	86	—	FECD	—
21	66	Cardiac arrest	12.2	7	Unknown	F	73	OD	FECD	20/40
22	62	Cardiac arrest	10.1	6	Unknown	M	71	OD	FECD	20/40
23	64	Pulmonary embolism	6.8	7	Optisol-GS	M	60	OS	FECD	20/20-1
24	68	Chronic obstructive pulmonary disease	18.0	4	Life4C	M	68	OS	FECD	20/60
25	54	Esophageal cancer	5.0	4	Optisol-GS	F	34	OD	FECD	20/50
26	64	Lung cancer	9.5	8	Optisol-GS	F	67	OS	FECD	20/40
27*	66	Cardiomyopathy	13.6	8	Optisol-GS	M	84	OD	FECD	20/30
28	86	Congenital heart defect	10.0	13	DMEM†	F	73	OS	FECD	20/80
29	68	Myocardial infarction	41.0	6	DMEM†	M	57	OD	FECD	20/50
30	69	Heart disease	12.0	13	Optisol-GS	F	61	OS	FECD	20/80
31	66	Hypertensive cardiogenic shock	17.4	7	Optisol-GS	M	58	OD	FECD	20/50
32	86	Cardiogenic shock	3.0	17	CorneaMax, CorneaJet	M	70	OD	Regraft	20/133
33	54	Cardiac arrhythmia	15.0	4	Optisol-GS	—	69	—	Other	—
34	69	Chronic obstructive pulmonary disease	17.0	7	Optisol-GS	—	67	OD	FECD	20/60

*Donor tissue pairs.
†Amphotericin B supplementation.
‡Life4C used for preservation media, Optisol-GS use for postprocessing media.
—, data not available; F, female; FECD, Fuchs endothelial corneal dystrophy; M, male.

Management

Information regarding clinical management was available for 27 of the 34 (79.4%) cases (Table 4). The most commonly administered routes of antifungal therapy were oral and/or intravenous, which were administered to all affected individuals, followed by intracameral in 25 (92.6%), topical in 24 (88.9%), intravitreal in 15 (55.6%), and intrastromal in 10 (37.0%) eyes. In 25 (92.6%) eyes, 3 or more different routes of antifungal agent administration were used. Information regarding the timing of the initiation of antifungal treatment was available for 24 eyes. Although 19 of 20 donor rim fungal cultures were positive, only 1 eye (case 4) was treated with prophylactic antifungal therapy in response to the positive donor rim fungal culture. In this case, topical voriconazole was initiated 2 days after DMEK surgery and 7 days before the presentation of endophthalmitis. Of the remaining 23 cases, the average time to first medical intervention was 2.0 ± 6.1 (median 0, range 0–29) days after clinical findings of infection were diagnosed, with treatment being initiated in 16 eyes on the day of diagnosis.

As multiple routes of antifungal agent administration were used in greater than 90% of eyes, it is not possible to determine the efficacy of each individual route of administration in eradicating infection and preventing the need for subsequent surgical intervention. Information regarding the timing of surgical intervention was available for 20 of 21

TABLE 3. Donor and Recipient Culture Information and Infection Presentation Among Eyes With Fungal Infection After Descemet Membrane Endothelial Keratoplasty

Case Number	Donor Culture Performed	Donor Culture Positive	Microorganism from Donor	Recipient Culture Performed	Recipient Culture Positive	Microorganism from Recipient	Days to Presentation	Infection Presentation
1	Yes	Yes	*C. glabrata*	Yes	Yes	*C. glabrata*	83	Endophthalmitis
2	No	NA	NA	Yes	Yes	*C. albicans*	24	Endophthalmitis
3	No	NA	NA	Yes	Yes	*C. glabrata*	8	Endophthalmitis
4	Yes	Yes	*C. albicans*	Yes	Yes	*C. albicans*, *C. glabrata*	9	Endophthalmitis
5	Yes	Yes	Yeast	Yes	Yes	*C. glabrata*	48	Endophthalmitis
6	Yes	Yes	*C. albicans*, *C. dubliniensis*	Yes	No	NA	7	Keratitis
7	Yes	Yes	*C. albicans*	Yes	Yes	*C. albicans*	Unknown	Keratitis
8	No	NA	NA	Yes	Yes	*C. albicans*	34	Endophthalmitis
9	No	NA	NA	Yes	Yes	*Purpureocillium lilacinum*	24	Endophthalmitis
10	No	NA	NA	Yes	Yes	*C. albicans*	64	Keratitis
11	Yes	Yes	*C. glabrata*	No	NA	NA	26	Keratitis
12	Yes	Yes	*C. tropicalis*	Yes	Yes	*C. tropicalis*	2	Endophthalmitis
13	Yes	Yes	*C. tropicalis*	Yes	Yes	*C. tropicalis*	2	Endophthalmitis
14	Yes	Yes	*C. guilliermondii*	Yes	Yes	*C. parapsilosis*	16	Keratitis
15	No	NA	NA	Yes	Yes	*C. glabrata*	32	Endophthalmitis
16	Yes	No	NA	Yes	Yes	*C. glabrata*	15	Keratitis
17	No	NA	NA	Yes	Yes	*C. glabrata*	23	Keratitis
18	Yes	Yes	*C. other*	Yes	No	NA	18	Keratitis
19	No	NA	NA	Yes	Yes	*C. glabrata*	47	Endophthalmitis
20	No	NA	NA	Yes	Yes	*C. glabrata*	47	Endophthalmitis
21	No	NA	NA	Yes	Yes	*C. glabrata*	35	Endophthalmitis
22	No	NA	NA	Yes	Yes	*C. parapsilosis*	82	Endophthalmitis
23	Yes	Yes	*C. albicans*	No	*NA*	*NA*	3	Endophthalmitis
24	Yes	Yes	*C. albicans*	Yes	No	NA	22	Endophthalmitis
25	No	NA	NA	Yes	Yes	*C. glabrata*	5	Endophthalmitis
26	Yes	Yes	*C. albicans*, *C. dubliniensis*	Yes	Yes	*C. parapsilosis*	949	Endophthalmitis
27	No	NA	NA	Yes	Yes	*C. albicans*, *C. glabrata*	57	Endophthalmitis
28	Yes	Yes	*C. orthopsilosis*	No	NA	NA	13	Endophthalmitis
29	Yes	Yes	*C. albicans*	No	NA	NA	5	Endophthalmitis
30	Yes	Yes	*C. albicans*	No	NA	NA	4	Endophthalmitis
31	No	NA	NA	Yes	Yes	*Candida spp*	70	Endophthalmitis
32	Yes	Yes	*C. albicans*	Yes	Yes	*C. albicans*	12	Endophthalmitis
33	Yes	Yes	*C. glabrata*	Yes	Yes	*C. glabrata*	200	Keratitis
34	Yes	Yes	*C. glabrata*	Yes	Yes	Yeast	24	Endophthalmitis

C., Candida; NA, not applicable.

eyes. The mean time from presentation of infection to the first surgical intervention was 61 ± 126 days, with surgical intervention being performed within the first week in 9 eyes and more than a year after the diagnosis of infection in 2 eyes (cases 21 and 22). Overall, surgical intervention was performed in 21 (77.8%) eyes, most commonly in the form of DMEK graft removal (partial or complete) in 11 (40.1%; 9 complete, followed by EK in 6 and penetrating keratoplasty (PK) in 3; 2 partial) eyes, therapeutic PK in 10 (37.0%) eyes, repeat EK in 8 (29.6%; 6 DMEK and 2 DSEK) eyes, and pars plana vitrectomy in 5 (18.5%) eyes. One eye (case 22) also underwent intraocular lens exchange at the time of vitrectomy, and another eye (case 34) underwent intraocular lens implant removal with subsequent replacement.

In the initial treatment approach, the original DMEK graft interface was removed (partial or complete removal separate from subsequent EK or PK) in 3 eyes and left in place (medical therapy only or pars plana vitrectomy) in 22 eyes or replaced (EK exchange) in 2 eyes. The percentage of eyes that required subsequent surgical intervention (not including a single EK or PK after DMEK graft removal) was significantly lower after removal of the EK interface (0%,

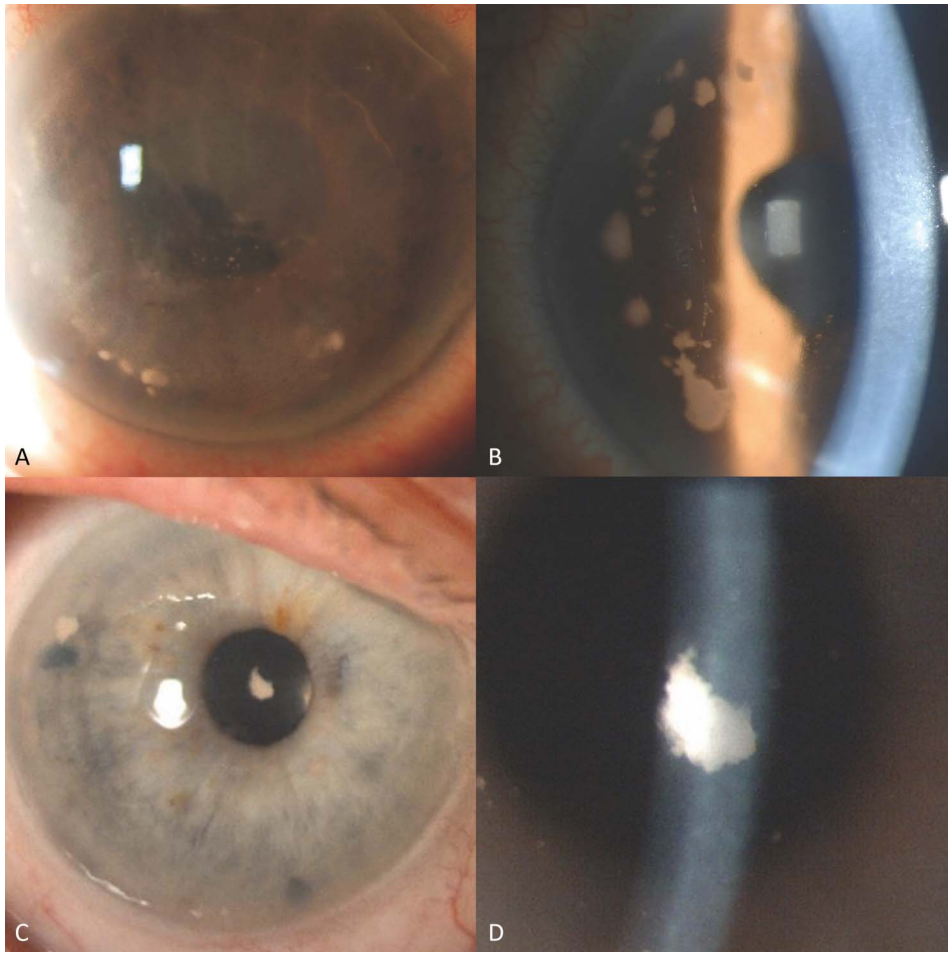

FIGURE 1. Fungal keratitis after Descemet membrane endothelial keratoplasty. Slit lamp images of: case 3 on postoperative day 8, the day of infection presentation with interface opacities (A), and postoperative day 26 after the initiation of topical, intracameral, and oral antifungal treatment (B); and case 10 on postoperative day 64, the day of presentation of discrete central and peripheral interface opacities (C, D). Photographs courtesy of Bowes Hamill, MD (A, B) and Nicola Lau, MD (C, D).

0/3) compared with eyes without removal of the EK interface (70.8%, 17/24) ($P = 0.04$). When the initial surgical approach was evaluated, the percentage of eyes in which subsequent surgical intervention (not including a single EK or PK after DMEK graft removal) was needed was significantly lower in the eyes that underwent removal of the original DMEK graft interface (13.3%, 2/15 eyes) compared with eyes in which the interface was left in place or replaced (83.3%, 5/6 eyes) ($P = 0.006$). In each of the 9 eyes in which a complete DMEK graft removal was performed separately from graft replacement, subsequent EK (6 eyes) or PK (3 eyes) was performed. None of the eyes in which repeat EK was performed, either as a primary surgical procedure or after DMEK graft removal, required PK.

Outcomes

Final Corrected Distance Visual Acuity

For the 27 cases for which information regarding clinical outcomes was available, the average length of follow-up was 22 ± 20 (median 11, range 4–69) months after the initial DMEK procedure (Table 5). At the last follow-up, 21 eyes (77.8%) had a CDVA of ≥20/200, 13 eyes (48.1%) had a CDVA of ≥20/40, and 9 eyes (33.3%) had loss of 2 or more Snellen acuity lines from preoperative CDVA. Six eyes (22.2%) had an acuity level of counting fingers (n = 3), light perception (n = 2), or no light perception (n = 1). The final CDVA ranged from 20/20 to light perception, with an average logMAR CDVA for all eyes of 0.70 ± 0.81 (approximately 20/100).

Although an analysis of the relationship between systemic antifungal administration and visual acuity outcomes could not be performed because this route of administration was used in all or all but one case, neither topical ($P = 0.55$), intrastromal ($P = 1.00$), intracameral ($P = 0.40$), nor intravitreal ($P = 0.18$) administration was associated with the percentage of eyes with a final CDVA ≥20/200. For eyes that underwent surgical treatment with data available regarding the timing of surgical interventions, there was a nonsignificant trend toward a higher percentage of eyes with a final CDVA ≥20/200 that received surgery within the first week after infection presentation (9/9, 100%) versus later (7/11, 63.6%, $P = 0.094$). There was no significant difference in the percentage of eyes with a final CDVA ≥20/200 when comparing eyes in which the graft interface was removed versus retained as the initial surgical approach ($P = 0.60$) or in which the graft interface was removed at any time during treatment ($P = 1.00$). However, a significantly higher percentage of eyes of patients who did not require additional surgery (other than a single EK or PK after

TABLE 4. Medical and Surgical Interventions for Fungal Infections After Descemet Membrane Endothelial Keratoplasty

	Medical Intervention					Surgical Intervention			
Case Number	Topical	Intrastromal (# of Injections)	Intracameral (# of injections)	Intravitreal (# of Injections)	Systemic	DMEK Explant	Repeat EK	PK	PPV
1	Ampho	Vori	Ampho (20), Vori (20)	Ampho (3), Vori (3)	Pos PO	No*	No	No	Yes
2	Ampho	—	Ampho (5)	Ampho (5)	Flu PO and IV, Vori PO and IV	Yes	DSEK	No	No
3	Ampho, Nata	—	Ampho (7)	Ampho (8), Vori (7)	Vori PO	No	No	No	Yes
4	Vori	—	Ampho (11), Vori (13)	Vori	Vori PO	Yes	DSEK	No	No
5	Vori	Vori	Ampho, Vori (3)	Ampho (2), Vori (3)	Flu PO, Vori PO	Yes	No	Yes	No
6	Vori	Vori	Ampho	—	Flu PO	No	No	Yes	No
8	Ampho, Chlorhex, Nata	—	Ampho (2)	—	Flu PO	Yes	DMEK	No	No
9	Nata	—	Ampho	Ampho	Vori PO	No	No	Yes	No
10	Ampho, Chlorhex	—	Ampho	—	Flu PO	Yes	DMEK	No	No
11	Vori	Ampho (2)	Ampho	—	Flu PO	No	No	No	No
12	Ampho, Vori	—	Ampho, Vori	—	Vori IV	No	DMEK	No	No
13	Ampho, Vori	—	Ampho, Vori	Ampho	Vori IV	No	DMEK	No	Yes
14	Ampho, Vori	Vori (3)	Vori (5)	—	Vori IV	No	No	No	No
15	—	—	—	Ampho (4), Vori (6)	Vori PO	No	No	No	No
21	Vori	—	Ampho, Vori	—	Vori PO	No	No	Yes × 4	No
22	Vori	Vori	Ampho, Vori	Vori	Vori PO	No	No	Yes	Yes
23	Ampho	—	Ampho, Vori (6)	—	Vori PO	No†	No	No	No
24	Ampho	Ampho, Vori	Ampho, Vori	Ampho, Vori	Pos PO	No*	No	No	No
25	Ampho, Vori	—	Ampho	Ampho (2), Vori	Flu PO	Yes	DMEK × 2	No	No
26	—	Ampho	Ampho	—	Flu PO	No	No	Yes	No
27	Ampho, Nata	—	Ampho (3)	Ampho	Flu PO, Vori PO	Yes†	DMEK	No	No
28	Ampho, Vori	—	Ampho, Vori (2)	—	Flu IV, Vori IV	No	No	No	No
29	Ampho, Nata, Vori	—	Ampho (2), Vori (3)	—	Flu IV	No	No	No	No
30	Ampho, Vori	—	Ampho (4), Vori (4)	Ampho, Vori	Vori IV	Yes	No	Yes	No
31	Ampho	Vori	Vori	Vori	Flu PO	Yes	No	Yes	No
32	Flu	Flu	Flu	—	Flu PO	No	No	Yes	No
34	—	—	—	Ampho (3), Micafungin (3), Vori (3)	Vori PO	No	No	Yes	Yes

*Affected area of graft selectively excised.
†Graft detachment rebubbled.
—, none; Ampho, amphotericin B; Chlorhex, chlorhexidine; Flu, fluconazole; IV, intravenous; Nata, natamycin; PO, per oral; Pos, posaconazole; PPV, pars plana vitrectomy; Vori, voriconazole.

DMEK graft removal) after the initial surgery had a final CDVA ≥20/200 (92.9%, 13/14) compared with those who did (42.9%, 3/7) ($P = 0.025$).

Recurrence of Infection

Fungal infection recurred in 6 cases (cases 13, 14, 21, 22, 25, and 28). Recurrence occurred as early as 1 and as late as 53 months after apparent resolution of infection. Four (66.7%) recurrences developed after both medical and surgical treatment of the initial infection, whereas 2 (33.3%) developed after medical treatment only. Recurrence of infection was not observed after partial or complete DMEK graft removal in any of the 11 eyes in which it was performed. However, infection recurred in 2 of the 10 eyes (20.0%) that underwent PK despite the graft diameter encompassing the affected cornea in each case. Recurrence was effectively treated medically in 2 (33.3%) eyes, surgically in 2 (33.3%) eyes, and with both medical and surgical approaches in 1 (16.7%); treatment continues in 1 eye, 5.5 years after the initial infection presentation.

Donor Mate Culture Results and Recipient Outcomes

Six of the 34 cases of fungal infection after DMEK that we report are mated corneas (cases 10 and 27, 12 and 13, and 19 and 20). Therefore, for the purpose of determining the

TABLE 5. Available Surgical, Microbiological, and Clinical Course Information of Cases of Fungal Infection After Descemet Membrane Endothelial Keratoplasty

Case Number	Clinical Course	Recurrence	Time to Final Follow-up (mo)	Final CDVA
1	Topical, intrastromal, intracameral, intravitreal antifungals → PPV + selective excision of plaque and underlying graft + oral antifungals	No	7.8	20/25
2	DMEK removal for primary graft failure and keratic precipitate noted → topical, intracameral, intravitreal, oral, IV antifungals → DSEK	No	9.7	20/80
3	Topical, intracameral, intravitreal, oral antifungals → PPV + intravitreal voriconazole → retinal detachment and repair with intravitreal injections → culture negative after 8 mo	No	8.6	CF
4	Topical, intracameral, intravitreal, oral antifungals → DMEK removal + intracameral injections → DSEK 4 months later → interface haze remained	No	52.5	20/60
5	Topical, intracameral, intravitreal, oral antifungals → DMEK removal + intracameral and intravitreal amphotericin B + intrastromal voriconazole + anterior chamber washout + synechialysis → PK	No	6.1	LP
6	Topical, intrastromal, intracameral, oral antifungals → PK	No	40.1	20/30
8	Topical, intracameral antifungals + DMEK removal → oral fluconazole → DMEK 4 mo later	No	39.4	20/30
9	Topical, intracameral, intravitreal, oral antifungals → PK → secondary glaucoma treated with an Ahmed valve	No	5.0	CF
10	Topical, intracameral, oral antifungals + DMEK removal + anterior chamber washout → DMEK 4 mo later	No	10.0	20/40
11	Topical, intrastromal, intracameral, oral antifungals	No	7.3	20/25*
12	Topical, intracameral, IV antifungals + DMEK-for-DMEK exchange	No	4.0	20/50
13	Topical, intracameral, IV antifungals + DMEK-for-DMEK exchange → fungal endophthalmitis 6 months later → vitrectomy and intravitreal amphotericin B	Yes	11.0	20/200
14	Topical, intrastromal, intracameral, IV antifungals → recurrence of fungal interface keratitis after 6 weeks → topical and intracameral injections → intrastromal voriconazole × 3	Yes	5.9	20/50
15	Intravitreal and oral antifungals	No	8.4	NLP
21	Topical, oral antifungals → intracameral injections → PK × 4 for recurrence at 16, 26, 38, and 53 mo after first infection	Yes	52.9	LP
22	Topical, oral, intracameral voriconazole → PPV + IOL extraction + intrastromal and intravitreal voriconazole at 11 months → PK at 31 mo → anterior chamber fluid culture positive for *C. parapsilosis* at 39 mo after initial infection → intracameral amphotericin and voriconazole → PK planned	Yes	69.2	CF
23	Topical, intracameral, oral antifungals	No	15.3	20/20−*
24	Topical, oral antifungals → intracameral amphotericin, voriconazole → selective excision of hypopyon and underlying graft → intrastromal and intravitreal amphotericin and voriconazole		5.5	20/40 + 2
25	Topical amphotericin B → intravitreal amphotericin → intravitreal amphotericin + intracameral amphotericin, voriconazole → DMEK-for-DMEK exchange → topical voriconazole → recurrence 1 mo post-DMEK → DMEK removal + intracameral and intravitreal voriconazole → 6 wk oral and topical antifungals → DMEK	Yes	7.2	20/25

TABLE 5. (*Continued*) Available Surgical, Microbiological, and Clinical Course Information of Cases of Fungal Infection After Descemet Membrane Endothelial Keratoplasty

Case Number	Clinical Course	Recurrence	Time to Final Follow-up (mo)	Final CDVA
26	Intrastromal, intracameral amphotericin B → oral fluconazole → PK	No	51.9	20/25
27	Topical, intracameral, oral antifungals → DMEK removal + intravitreal, intracameral amphotericin → topical amphotericin → oral, intracameral antifungals → repeat DMEK 7 mo later	No	46.8	20/120
28	Topical, intracameral, oral antifungals → recurrence at 1 mo → intracameral injections × 4 wk	Yes	32.0	20/20
29	Topical, intracameral, IV antifungals	No	48.0	20/20
30	Topical, IV antifungals → DMEK removal and vitreous aspiration + intravitreal antifungals → intracameral amphotericin and voriconazole × 4 → PK 2 mo later	No	24.0	20/50
31	Topical, intrastromal, intracameral, intravitreal, oral antifungals → DMEK removal + intrastromal, intracameral, intravitreal voriconazole → intrastromal, intracameral, intravitreal voriconazole → PK → continued topical and oral antifungals	No	5.5	20/100
32	Topical, intracameral, and oral fluconazole → DMEK removal + anterior chamber washout + PK + intrastromal fluconazole → topical fluconazole → oral fluconazole	No	12.0	20/20
34	Oral voriconazole → intravitreal voriconazole → IOL and capsular bag removal + intravitreal voriconazole → intravitreal voriconazole → intravitreal amphotericin B × 2 → DMEK removal + PK + PPV + intravitreal amphotericin B → intravitreal micafungin × 3 → IOL placement	No	12.4	20/40

*Uncorrected visual acuity.
→, passage of an interval of time; CF, counting fingers; IOL, intraocular lens; IV, intravenous; LP, light perception; NLP, no light perception; PPV, pars plana vitrectomy.

status of the donor mates of the corneas that resulted in donor infection after DMEK, we included one of the mated corneas from each of these donors (cases 13, 20, and 27). Information on donor tissue mate preparation, surgery, culture, or infection was available for 28 of the remaining 31 (90.3%) cases (see Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/ICO/B423). The average death to preservation time among these 28 donor mates was 12.7 ± 10.4 (median 10.0, range 3–41) hours and death to surgery time was 6.9 ± 2.6 (median 6, range 4–14) days. Donor rim fungal cultures were performed for 12 of 27 (44.4%) mated corneas (missing data: 1), with 6 (50.0%) positive, all for *C. spp* that were concordant with the species identified in the mated donor cornea rim fungal culture and/or the recipient culture. Twenty-four of the mated corneas were transplanted, 3 were not transplanted (2 grafts damaged during processing and 1 for unknown reason), and the status of 1 mate cornea is unknown. Ten of the mated corneas were used for EK (7 for DMEK and 3 for DSEK), 2 were used for PK, and the type of keratoplasty performed using the other 12 mated corneas is unknown. Seventeen (70.8%) of the recipients of the mated corneas had an uncomplicated postoperative course, whereas 7 (29.2%) experienced a postoperative complication: 4 endophthalmitis, 2 keratitis, and 1 primary graft failure (n = 1). Of the 10 mated corneas used for EK, 5 (50.0%) of the recipients developed either endophthalmitis (n = 4) or keratitis (n = 1). Of the 7 recipients of corneas with positive donor rim fungal cultures, 3 (42.9%) developed endophthalmitis (n = 2) or keratitis (n = 1).

DISCUSSION

This study presents the largest compilation to date of fungal keratitis and endophthalmitis after DMEK, including 14 published and 20 unpublished cases. Although the sample size remains small, the cohort offers valuable insight into the incidence, presentation, management, and outcomes of fungal infections after DMEK.

Incidence and Presentation of Fungal Infection After DMEK

The observed incidence of fungal keratitis and endophthalmitis based on the OARRS database for the period spanning from 2011 to 2021, during which 60,042 DMEK procedures were performed, was 0.013% and 0.022%, respectively. Augustin et al[11] reported an incidence rate of 0.15%, corresponding to the development of 6 cases of interface fungal keratitis in 3950 DMEK procedures, which is 10 times higher than our calculated incidence based on the OARRS data. However, it is likely that in the absence of stringent rules that mandate the reporting of infectious complications, these figures underestimate the total number and the actual incidence rate of fungal infections after DMEK.

The peak incidence of fungal infections was observed in 2014, which coincides with the peak incidence of fungal infections after DSEK, as reported in previous studies.[2,3] However, in contrast to reports of an increasing incidence of postkeratoplasty fungal infection before 2014, we did not identify a significant increase in the incidence of fungal infection after DMEK between 2011 and 2020.

The 0.035% incidence of fungal infection after DMEK that we report is higher than that reported after DSEK and PK. Studies from the EBAA of adverse reactions after keratoplasty reported a 0.022% incidence of fungal infection after DSEK and 0.012% after PK between 2007 and 2010 and an incidence of 0.041% after EK (mostly DSEK, 57 cases of fungal infections with only 3 cases reported after DMEK) and 0.012% after PK between 2007 and 2014.[2,3] Single-institution studies have described higher rates of postkeratoplasty fungal infection of 0.16% after PK[16] and 0.23% to 0.92% after DSEK.[5,17–19] The increased incidence of fungal infection after DSEK and DMEK compared with PK may be due to differences in graft processing. EK grafts also require more extensive preparation that involves warming, generating greater opportunity for fungal proliferation.[20,21] A notable risk factor inherent to EK procedures is the creation of a host–graft tissue interface. Although lamellar keratoplasty (LK) procedures require a much smaller opening and potential mycotic entry point than PK, the host–graft tissue interface creates a potential space within which fungi can multiply but neither immune cells nor therapies can readily access.[5,22,23]

Management

Lamellar keratoplasty-related infections can be particularly challenging from a therapeutic standpoint because the intracorneal host–graft interface is sequestered from immune surveillance and drug penetration.[22] Although post-DSEK fungal infections successfully treated by medical treatment alone have been reported,[6] most require surgical intervention and ultimately undergo PK.[4,5,24] Similarly, we report that more than 3 quarters of post-DMEK fungal infections require surgical intervention, although most eyes did not require PK. As it has been proposed that the decreased thickness of a DMEK graft compared with a DSEK graft may allow for increased drug delivery to the interface after an intracameral injection,[8] we examined whether intracameral injections of antifungal medications were effective at eradicating infection and thus preventing the need for subsequent surgical intervention. Our finding that most eyes that received an intracameral injection of amphotericin B, fluconazole, voriconazole, or a combination thereof required subsequent surgical intervention indicates that intracameral antifungal therapy is usually not sufficient to eradicate interface fungal infection after DMEK.

Removal of the DMEK graft interface, either with DMEK explantation alone or through the performance of PK, as either the initial treatment approach or the initial surgical intervention, was associated with a significant reduction in the percentage of eyes that required subsequent surgical intervention compared with eyes in which the interface was left in place or replaced. In addition, the percentage of eyes with a final CDVA $\geq$ 20/200 was significantly higher in the group that did not require additional surgery after an initial surgical intervention. Although there is a concern regarding spreading of what was a sequestered interface infection into the anterior chamber after explantation of a DMEK graft, none of the 11 eyes in which this was performed developed a recurrence of infection. By contrast, 4 of the 10 eyes in which the surgical intervention consisted of repeat EK (2/3 eyes) or PK (2/7 eyes) (not after a separate DMEK graft explantation) developed a recurrence of infection. As an example, in case 25, the initial DMEK-for-DMEK exchange was followed by infection recurrence, which resolved after DMEK removal and intracameral and intravitreal voriconazole injections before a third DMEK graft 6 weeks later. Therefore, we recommend removal of the interface in cases of interface fungal keratitis after DMEK that are not responsive to medical therapy.

Outcomes

Although the previously reported visual outcomes of fungal infection after DMEK are generally encouraging, with 92.9% (13/14) of eyes having a final CDVA $\geq$20/200 and 50.0% (7/14) of eyes having a final CDVA $\geq$ 20/40, the inclusion of previously unreported cases in this report provides a more guarded visual prognosis. Fewer than half the eyes had a final CDVA of 20/40 or better, and notably almost a quarter had a final CDVA of counting fingers or worse. The mean final CDVA of 0.70 logMAR, corresponding to approximately 20/100, is also notably worse than the mean final CDVA of 0.44 logMAR, or approximately 20/55, reported after the resolution of 24 cases of fungal infection after DSEK.[4]

As is a limitation with any retrospective case series, it remains to be determined whether any associations between the timing and type of treatment for fungal infection after DMEK and the observed outcomes are reflective of a treatment selection bias, confounding factors that may influence outcomes, the effectiveness of the treatment(s), or a combination thereof. Further complicating efforts to develop evidence-based guidelines to managing fungal infection after DMEK are the small number of cases available for analysis, the use of multiple treatments in each case, and the use of some treatments in all cases and others in only a small percentage of cases. However, given the low incidence of fungal infection after DMEK, a randomized controlled trial to determine the most effective treatment regimen is not feasible. Therefore, it remains to be seen whether surgical intervention is a marker of greater disease severity, used in more advanced cases and associated with poorer outcomes, or is in fact a therapeutic approach that if performed in a timely manner leads to improved outcomes. Regarding specific medical and surgical treatment approaches, whether a particular medication, route of administration, procedure, or combination is most effective is still unclear. Because intrastromal injections can place a high concentration of drug near the graft–host interface, unlike other delivery methods that require diffusion into the cornea, they may have particular

relevance in treating interface infection after EK procedures.[6,9] Similarly, we agree with others who have advocated for the removal of the interface in cases of interface fungal infection after lamellar keratoplasty.[4,25] Although some authors advise earlier surgical intervention in cases of interface fungal keratitis, and the data that we present suggest that earlier surgical intervention may result in better final visual outcomes, the number of cases is too limited to make any recommendations regarding whether and how long medical therapy should be used before surgical treatment.[8,10,11,13]

Utility of Donor Rim Fungal Cultures and Antifungal Prophylaxis

The correlation of a positive donor rim fungal culture and an increased risk of fungal infection developing in the recipient is well established, with the percentage risk estimated to be approximately 11% in a recently published review.[26–29] Although there are no prospective studies that have examined the efficacy of prophylactic antifungal therapy after the receipt of a positive donor rim fungal culture, a retrospective study of 71 eyes identified a 7-fold lower incidence of postkeratoplasty fungal infection after the receipt of a positive donor rim fungal culture in eyes that received topical and/or oral antifungal prophylaxis, although the result was not statistically significant.[30] If a donor rim fungal culture is not performed, antifungal therapy would not be initiated until keratitis or endophthalmitis had already developed, which was more than 1 month after DMEK surgery in 40% of eyes in this series. Assuming that the time to initiation of treatment for infection is associated with outcomes, as is generally accepted for treatment of bacterial keratitis and endophthalmitis, the delay in treatment that results from not performing a donor rim fungal culture, or not initiating prophylactic antifungal therapy after the receipt of a positive donor rim fungal culture, could lead to a more protracted treatment course and worse outcomes. Given these considerations, as well as the fact that antifungal prophylaxis after the receipt of a positive donor rim fungal culture has been shown to be cost-effective if the contamination risk is sufficiently high, we agree with others who have advocated for the routine performance of donor rim fungal cultures and the prompt initiation of antifungal prophylaxis in the event of a positive donor rim fungal culture.[24,30–32] This series, in which donor rim fungal cultures were performed in less than 60% of cases and prophylactic antifungal therapy was initiated in only a single case, and in which surgical intervention was required in more than 75% of cases with a final postoperative visual acuity of counting fingers or worse in approximately a quarter of eyes, clearly indicates the need to improve outcomes of fungal infection after DMEK.

Donor Mate Culture Results and Recipient Outcomes

The current study supports the findings of previously published series that reported an increased incidence of a positive donor rim fungal culture and postkeratoplasty fungal infection among the mates of corneas that transmitted a fungal infection to the recipient.[2] Given this, we recommend consideration of the institution of antifungal prophylaxis on notification of a mated donor cornea transmitting a fungal infection to the recipient. We also recommend consideration of antifungal prophylaxis on notification of a positive donor rim fungal culture in the mated cornea, especially if a donor rim fungal culture was positive or was not performed.

CONCLUSION AND PERSPECTIVES

The findings presented here underscore the fact that despite intervention, final visual acuity outcomes remain poor for many patients who develop fungal infection after DMEK. Surgeons should be aware of the need for surgical management and the protracted course of therapy in most cases. Continued collection of cases and analysis of interventions and outcomes are warranted to continue to monitor the incidence and develop guidelines for management of fungal infection after DMEK. Therefore, we strongly encourage surgeons who diagnose fungal infection after DMEK to report the adverse event to either the distributing or source eye bank and to provide treatment and outcome data to the EBAA, when such information is requested.

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