Report of the Eye Bank Association of America Medical Review Subcommittee on Adverse Reactions Reported From 2007 to 2014

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Purpose: To investigate the incidence of adverse reactions after corneal transplantation, reported to the Eye Bank Association of America.

Methods: Incidence of adverse reactions from January 1, 2007, to December 31, 2014, was analyzed.

Results: Of the 354,930 transplants performed in the United States, adverse reactions were reported in 494 cases (0.139%). Primary graft failure (PGF) predominated (n = 319; 0.09%) followed by endophthalmitis (n = 99; 0.028%) and keratitis (n = 66; 0.019%). The procedure type predominantly associated with PGF was endothelial keratoplasty (EK) in 56% (n = 180; 11 per 10,000 grafts), followed by penetrating keratoplasty (PK) in 42% (n = 135; 6.9 per 10,000 grafts). The procedure type predominantly associated with endophthalmitis and keratitis was EK in 63% (n = 104; 6.3 per 10,000 grafts) followed by PK in 34% (n = 56; 2.8 per 10,000 grafts), anterior lamellar keratoplasty in 1% (n = 2; 2.7 per 10,000 grafts), and keratoprosthesis in 1% (n = 2; 12.4 per 10,000 grafts). Although the incidence of PGF and endophthalmitis between PK and EK was noteworthy, the difference was not statistically significant (P = 0.098). Endophthalmitis-associated pathogens were isolated in 78% of cases: predominantly *Candida* species (65%), gram-positive organisms (33%), and gram-negative rods (2%). Keratitis-associated pathogens were isolated in 64% of cases: predominantly *Candida* species (81%), *Herpes simplex* virus (7%), gram-negative organisms (7%), and gram-positive organisms (5%).

Conclusions: PGF was the most commonly reported adverse reaction, disproportionately associated with EK. An increasingtrend in the rate of endophthalmitis and keratitis was observed, disproportionately associated with EK and *Candida* species.

Key Words: corneal transplantation, adverse reactions, primary graft failure, endophthalmitis, infectious keratitis, Eye Bank Association of America

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The Eye Bank Association of America (EBAA) monitors adverse reactions of corneal transplants that are potentially attributable to donor eye tissue, including infection and biologic dysfunction. The EBAA initiated an adverse reaction reporting system in 1990 and has used the Online Adverse Reaction Reporting System (OARRS) for reporting since 2004. EBAA Medical Standard M1.500 requires each distributing establishment to seek postoperative outcome information from the surgeon 3 to 6 months after transplant.

Adverse reaction information is forwarded to the source eye bank and submitted to the EBAA within 30 days of the first report. The eye bank tracks the mated donor cornea and reviews donor and recipient records and microbiological results of preimplant donor cultures and recipient cultures. The medical director of the source eye bank establishes imputability or determines the likelihood that the adverse reaction in the recipient can be attributed to the tissue.

A literature search regarding adverse reactions after corneal transplantation, revealed several publications reporting the incidence of post–penetrating keratoplasty of primary graft failure (PGF)[1–4] and endophthalmitis.[5–10] There was relative paucity of data reporting: (1) the incidence relative to the procedure type, comparing penetrating keratoplasty (PK), endothelial keratoplasty (EK), anterior lamellar keratoplasty (ALK), and keratoprosthesis (KPro); (2) the incidence of "other" adverse reactions, including infectious keratitis, inadvertent use of postrefractive surgery tissue, transmission of corneal dystrophy, and systemic infection; (3) the changing milieu of infectious pathogens associated with EK compared with PK.

Herein, our analysis of adverse reactions reported to the EBAA represents the efforts of the eye banking and transplant surgeon community to ensure safe and efficacious donor corneal tissue, in addition to monitoring trends and practice patterns.

METHODS

A retrospective review was performed of all adverse reactions reported to the EBAA through OARRS, for corneal transplants performed between January 1, 2007, and December 31, 2014. Data regarding the total number of corneal tissues distributed by U.S. eye banks were obtained from the EBAA Statistical Report from 2014.[11] Adverse reactions were categorized and defined as follows:

- PGF is a edematous graft present from the time of keratoplasty that does not clear after 8 weeks without an identifiable operative or postoperative complication or underlying recipient condition that would explain the biologic dysfunction.
- A graft-transmitted ocular infection caused by bacterial, fungal, viral, or *Acanthamoeba* etiologies and including infectious keratitis and endophthalmitis.
- Any systemic infection caused by a relevant communicable disease, such as human immunodeficiency virus (HIV), viral hepatitis, or Creutzfeldt–Jakob disease (CJD), that develops in a recipient, irrespective of whether it is suspected to be because of the donor tissue. The U.S. Food and Drug Administration defines "relevant" as a means of identifying disease transmission risk associated with certain human cell and tissue products.[12]
- Transmission of corneal dystrophy, degeneration, or ocular malignancy.
- Evidence of prior refractive surgery in the donor tissue inadvertently used during keratoplasty.

Data were summarized using descriptive statistics (median for time to onset and count and frequency for adverse reactions). Yearly and seasonal variations in incidence of adverse reactions were compared among different procedure types using χ^2 or Fisher exact test. Median time to onset between different fungal and bacterial infections was compared using Mann–Whitney test. All analyses were performed using SAS 9.4 (SAS Inc, Cary, NC) and a P-value <0.05 was deemed statistically significant.

RESULTS

When calculating incidence, we chose to use the "number of corneal grafts performed in the United States" as the denominator. The EBAA Medical Advisory Board had endorsed this approach, because of potential under-reporting of adverse reactions occurring internationally. EBAA data report a total number of 354,930 corneal grafts performed in the United States from 2007 to 2014. Table 1 illustrates the number of grafts increased incrementally each year, from a low of 39,391 in 2007 to a high of 48,229 in 2013.

With regards procedure type, the predominant corneal transplant performed in the United States was PK at 195,859 grafts (mean 24,482 per year), followed by EK at 164,563 grafts (mean 20,570 per year), and ALK at 7517 grafts (mean 940 per year). There was an incremental increase in EK procedures noted over this time period (Table 2).

Adverse Reactions

Of the 494 adverse reactions reported (Table 1), PGF was the most common (65%) followed by endophthalmitis (20%), infectious keratitis (13%), donor-to-host transmission of systemic infection (0.6%), donor corneal dystrophy or degeneration (0.4%), donor corneal refractive surgery (0.4%), iritis (0.2%), and residual stromal edema (0.2%).

Primary Graft Failure

Incidence

PGF was reported in 319 cases (mean 40 cases/year) for an incidence of 9 per 10,000 grafts performed in the United States (Table 1).

The procedure type predominantly associated with PGF was EK in 56% (n = 180) followed by PK in 42% (n = 135) and ALK in 1% (n = 3) of cases. Figure 1 illustrates the incidence data (per 10,000 grafts performed in the United States) relative to the procedure type. Although the incidence of PGF between PK (6.9 cases) and EK (11 cases) was noteworthy, the difference was not statistically significant ($P = 0.098$).

The mate cornea was transplanted in 281 of the 319 cases, with PGF occurring in 45 of the 281 (16%) recipient eyes. EK was the most common procedure type occurring in 27 (60%) of mated cases; tissue preparation was performed using the microkeratome by the eye bank in 25 cases and by the surgeon in 2 cases.

Donor Corneal Characteristics

The mean donor age was 54.5 years (range, 1 month to 86 years). The mean endothelial cell density was 2793 cells/mm^2 (range, 1961–6000 cells/mm^2). The mean death to preservation was 10.7 hours (range, 1–25 hours), and the mean death to surgery was 6.8 days (range, 1–243 days). The tissue used 243 days postmortem was a scleral graft preserved in 100% ethyl alcohol.

The most common donor cause of death in patients with PGF was heart disease in 32% (n = 103), cancer in 24% (n = 77), other in 13% (n = 43), trauma in 12% (n = 39), respiratory disease in 8% (n = 26), stroke in 8% (n = 24), and toxic/accident in 2% (n = 7).

Post-Keratoplasty Endophthalmitis

Incidence

Endophthalmitis was reported in 99 cases (mean 12 cases/year) for an incidence of 2.8 per 10,000 grafts performed in the United States (Table 2). The trend showed an increase from a low of 5 cases in 2007 to a high of 26 in 2013 ($P < 0.01$). The relative number of fungal infections likewise shows an increasing trend from a low of 2 cases in 2007 to a high of 16 cases in 2013 ($P < 0.05$). Figure 2 similarly illustrates an increasing incidence from a low of 1.3 in 2007 to a peak of 5.4 in 2013.

The seasonal variation showed a higher proportion of fungal infection in springtime as compared with fall, summer, and winter (52% vs. 38%, 41%, and 42%, respectively). However, this was not statistically significant ($P = 0.73$).

The median time to onset of endophthalmitis after corneal transplant was 14 days (range, 1–221). The median time for bacterial infection (2.5 days) was significantly shorter ($P < 0.05$) than fungal infection (33 days).

The procedure type predominantly associated with endophthalmitis was EK in 61% (n = 60) of cases followed by PK in 37% (n = 37), KPro in 1% (n = 1), and scleral graft in 1% (n = 1) of cases. Figure 3 illustrates the incidence data

TABLE 1. Incidence of Adverse Reactions (Per 10,000 Grafts) From 2007 to 2014

Year	Corneal Grafts*	Total ARs†	Total ARs Incidence‡	PGF Cases	PGF Incidence‡	Endophthalmitis and Keratitis Cases	Endophthalmitis and Keratitis Incidence‡
2007	39,391	45	11.4	36	9.1	8	2
2008	41,652	64	15.4	54	13	10	2.4
2009	42,606	69	16.2	52	12.2	17	4
2010	42,642	49	11.5	31	7.3	16	3.8
2011	46,196	53	11.5	36	7.8	16	3.5
2012	46,684	60	12.6	31	6.6	28	5.9
2013	48,229	68	14.1	30	6.2	35	7.3
2014	47,530	86	17.9	49	10.3	35	7.3
Total	354,930	494	13.9	319	9	165	4.6

*Number of corneal grafts performed in the United States from 2009 to 2014. Data for 2007 and 2008 include procedures performed both domestically and internationally.
†Total ARs is inclusive of cases reported with PGF (n = 319), endophthalmitis and keratitis (n = 165), scleral graft infection (n = 1), donor corneal dystrophy or degeneration (n = 2), donor corneal refractive surgery (n = 2), donor-to-host transmission of systemic infection (n = 3), iritis (n = 1), and residual stromal edema posttransplant (n = 1).
‡Per 10,000 grafts.
AR, adverse reaction.

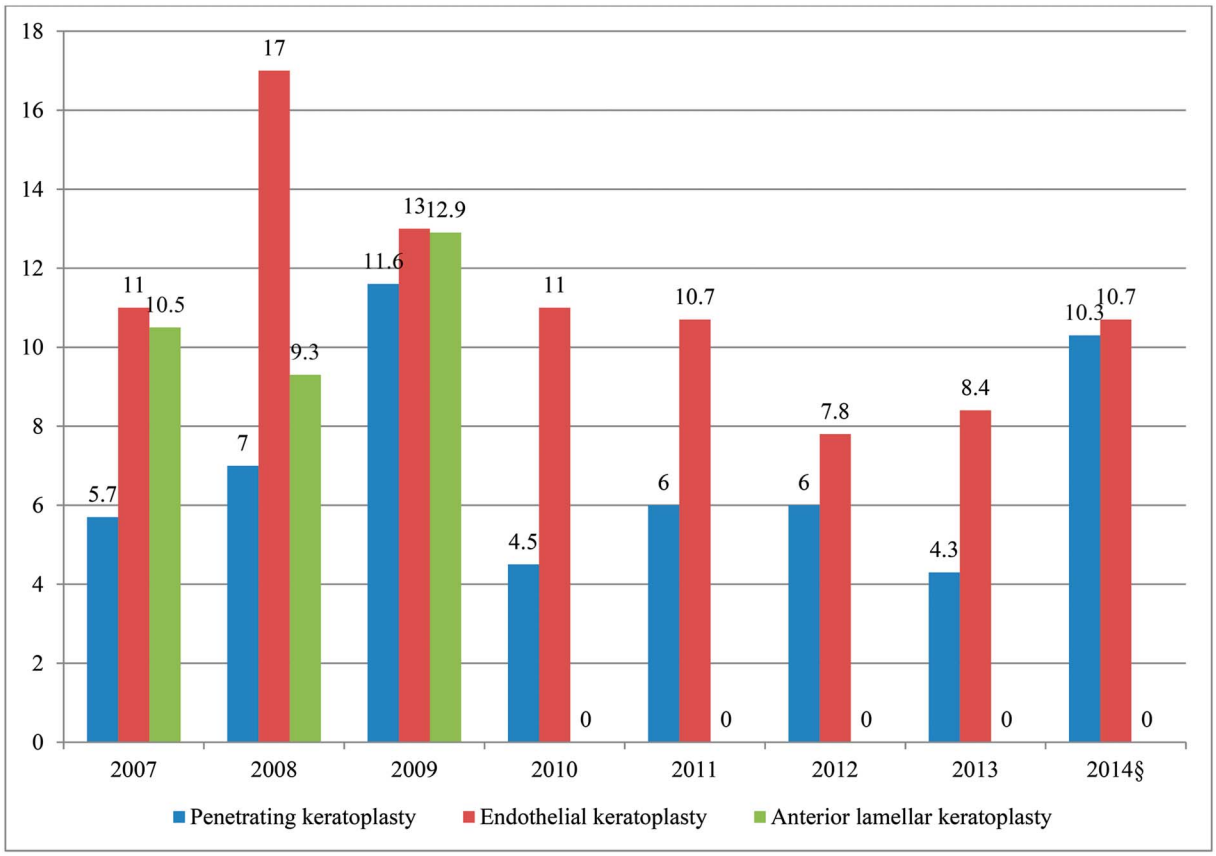
(per 10,000 grafts performed in the United States) relative to the procedure type. Although the incidence of endophthalmitis between PK (1.8 cases) and EK (3.6 cases) was noteworthy, the difference was not statistically significant ($P = 0.098$).

The mate cornea was transplanted in 86 of the 99 cases, with infection developing in 21 of the 86 (24%) recipient eyes: endophthalmitis in 20 eyes and keratitis in 1 eye. The concordance between matching recipient and mate culture in the 16 cases that had both cultures performed was as follows: *Candida* species in 75% (n = 12), *Enterococcus* species in 13% (n = 2), and *Clostridium perfringens* in 13% (n = 2). Culture was not performed in 4 of the recipient mates.

TABLE 2. Endophthalmitis and Keratitis Cases From 2007 to 2014: Incidence and Associated Procedure Type

	2007	2008	2009	2010	2011	2012	2013	2014	Total	Incidence*
Endophthalmitis										
All cases	5	6	7	10	10	19	26	16	99	2.8
Fungal cases	2	6	4	4	4	4	16	9	49	1.4
Keratitis										
All cases	3	4	10	6	6	9	9	19	66	1.8
Fungal cases	2	3	5	3	1	3	4	13	34	0.9
All infections										
All cases	8	10	17	16	16	28	35	35	165	4.6
Fungal cases	4	9	9	7	5	7	20	22	83	2.3
EK grafts†	14,159	17,468	18,221	19,159	21,555	23,049	24,987	25,965	164,563	
EK-related infections	2	4	7	9	10	20	24	28	104	6.3
Fungal cases	2	4	5	4	3	4	17	18	57	4.1
PK grafts†	34,806	32,524	23,269	21,970	21,620	21,422	20,954	19,294	195,859	
PK-related infections	6	6	9	5	4	8	11	7	56	2.8
Fungal cases	2	5	3	2	2	3	3	4	24	1.2
ALK grafts†	950	1072	774	1041	932	883	951	914	7517	
ALK-related infections	0	0	1	1	0	0	0	0	2	2.7
Fungal cases	0	0	1	1	0	0	0	0	2	2.7
KPro†	—	—	222	342	332	236	223	260	1615	
KPro-related infections	0	0	0	0	2	0	0	0	2	12.4
Fungal cases	0	0	0	0	0	0	0	0	0	0
Scleral graft–related infections	0	0	0	1	0	0	0	0	1	—
Fungal cases	0	0	0	0	0	0	0	0	0	—

EK includes descemet stripping EK.
*Per 10,000 grafts.
†Number of corneal grafts performed in the United States from 2009 to 2014. Data for 2007 and 2008 include procedures performed both domestically and internationally.
DMEK, descemet membrane EK.



§ In 2014 there was a single case of scleral graft-related primary graft failure.

Primary graft failure cases: 2007-2014	Penetrating keratoplasty (N=135)	Endothelial keratoplasty (N=180)	Anterior lamellar keratoplasty (N=3)
Mean incidence per 10,000 grafts	6.9	11	3.9

FIGURE 1. Incidence (per 10,000 grafts performed in the United States) of post-keratoplasty PGF relative to the procedure type, from 2007 to 2014.

Donor Corneal Characteristics

The mean donor age was 57 years (range, 13–75 years), mean death to preservation was 11 hours (range, 2–22 hours), and the mean death to surgery was 7 days (range, 2–128 days). The tissue used 128 days postmortem was a scleral graft preserved in sterile glycerin.

The most common donor cause of death in patients with endophthalmitis was heart disease in 34% (n = 33), other in 28% (n = 27), cancer in 15% (n = 15), respiratory disease in 14% (n = 14), trauma in 6% (n = 6), toxic/accident in 2% (n = 2), and stroke in 1% (n = 1).

Isolates

The causative pathogen was isolated in 78% (n = 77) of cases, no growth was reported in 10% (n = 10), and culture was not performed in 10% (n = 10) of cases. Table 3 illustrates the spectrum and frequency of organisms isolated, of which *Candida* species was the most common pathogen affecting 65% (n = 53) of cases.

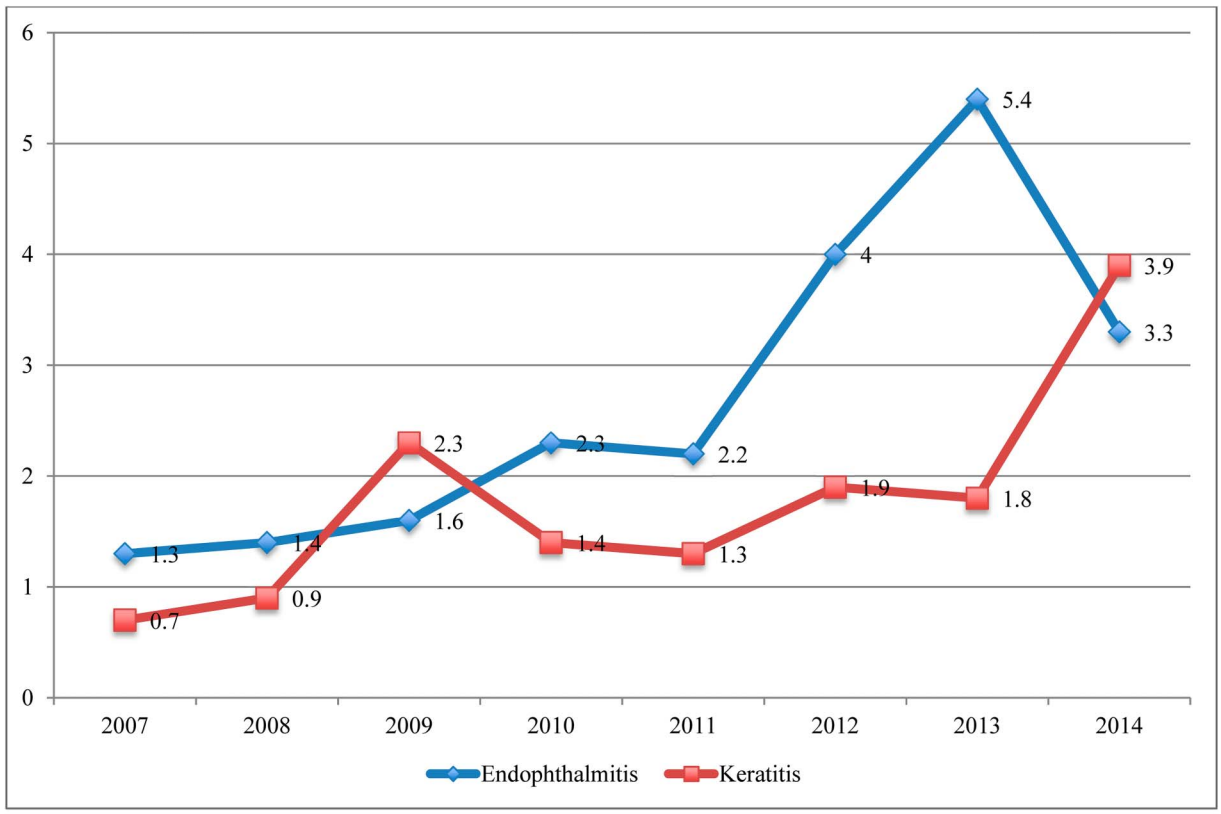
Post-Keratoplasty Infectious Keratitis

Incidence

Infectious keratitis was reported in 66 cases (mean 8 cases/year) for an incidence of 1.8 per 10,000 grafts performed in the United States. Table 2 illustrates an increasing trend from a low of 3 cases in 2007 to a high of 19 cases in 2014. The number of fungal infections likewise shows an increasing trend from a low of 2 cases in 2007 to a high of 13 cases in 2014. Figure 2 illustrates an increasing incidence from a low of 0.7 in 2007 to a high of 3.9 in 2014.

The seasonal variation showed a higher proportion of fungal infection in wintertime as compared with spring, summer, and fall (69% vs. 50%, 37%, and 55%, respectively). However, this was not statistically significant ($P = 0.30$).

The median time to onset of infectious keratitis after corneal transplant was 29 days (1–216 days) for all 66 cases. Fungal infection keratitis (n = 34) had a significantly longer time ($P < 0.05$) to onset of 45 days (3–216 days) compared



Post-keratoplasty infections 2007-2014	Endophthalmitis (N=99)	Infectious keratitis (N=66)
Mean incidence per 10,000 grafts	2.8	1.8

FIGURE 2. Incidence (per 10,000 grafts performed in the United States) of postkeratoplasty endophthalmitis and infectious keratitis cases, from 2007 to 2014.

with bacterial keratitis (n = 5) of 6 days (1–125 days) and herpes simplex keratitis (n = 3) of 24 days (16–30 days).

The procedure type predominantly associated with infectious keratitis was EK in 67% (n = 44) followed by PK in 29% (n = 19), ALK in 3% (n = 2), and KPro in 2% (n = 1). Figure 4 illustrates the incidence data (per 10,000 grafts performed in the United States) relative to the procedure type. The incidence data should be interpreted in context of a low number of KPro and ALK procedures being performed, compared with EK and PK.

The mate cornea was transplanted in 62 of the 66 cases, with infection developing in 12 of the 62 (19%) recipient eyes: endophthalmitis in 1 eye and keratitis in 11 eyes. The concordance between matching recipient and mate culture in the 8 cases that had both cultures performed was 100% (n = 8) for *Candida* or yeast species. Culture was not performed in 3 of the recipient mates.

Donor Corneal Characteristics

The mean donor age was 51.4 years (range, 2–74 years), mean death to preservation was 10.1 hours (range, 1.7–22 hours), and the mean death to surgery was 5.1 days (range, 2–13 days).

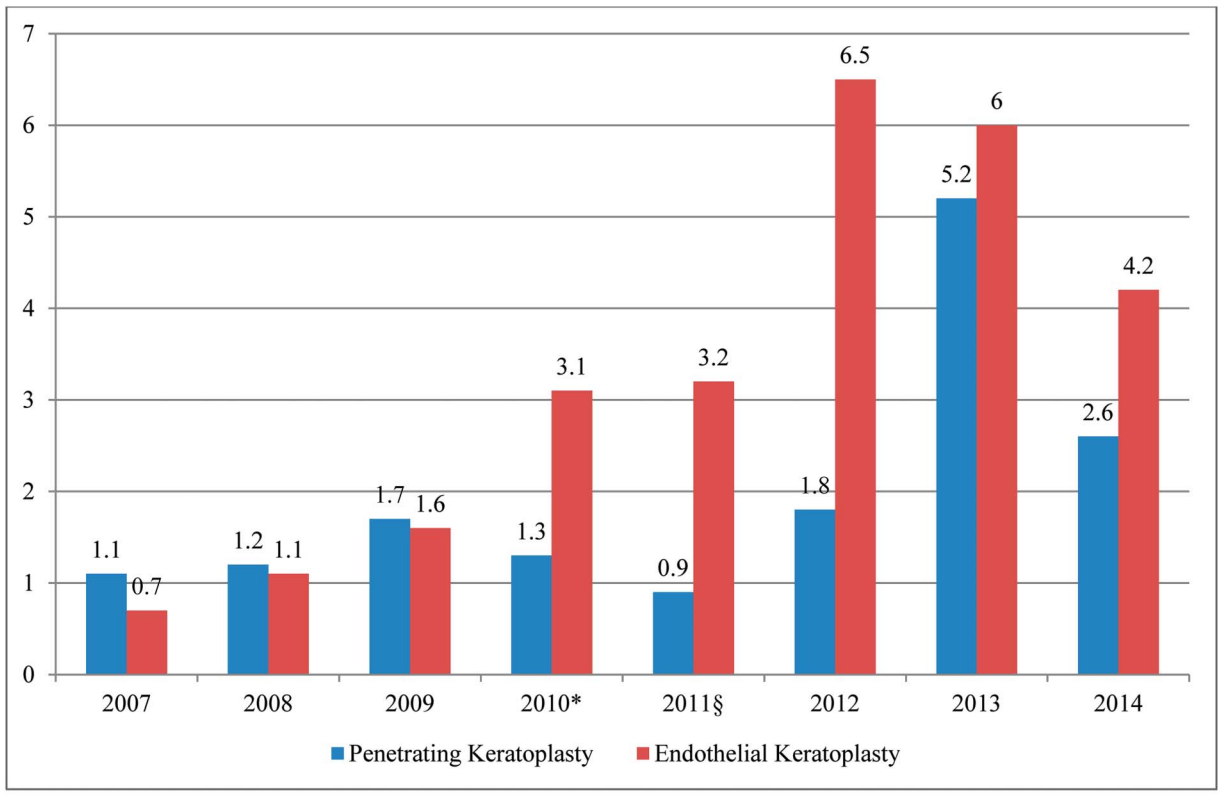
The most common donor cause of death in patients with keratitis was heart disease in 42% (n = 27), other in 17% (n = 11), cancer in 15% (n = 10), trauma in 15% (n = 10), stroke in 5% (n = 3), respiratory disease in 3% (n = 2), and toxic/accident in 3% (n = 2).

Isolates

The causative pathogen was isolated in 64% (n = 42), no growth reported in 12% (n = 8), and culture not performed in 23% (n = 15) of cases. Table 4 illustrates the spectrum and frequency of organisms isolated, of which *Candida* species was the most common pathogen, affecting 81% (n = 34) of cases. Notably, all cases of herpes simplex virus (HSV) keratitis (n = 3) were diagnosed clinically by characteristic examination findings and response to antiviral treatment. There was no serologic confirmation or a history of prior HSV infection noted.

OTHER ADVERSE REACTIONS

Donor-to-host transmission of systemic infection was reported in 3 cases; however, the final determination after investigation in conjunction with the Centers for Disease



* In 2010 there was a single case of scleral graft-related endophthalmitis.
§ In 2011 there was a single case of KPro-related endophthalmitis.

Endophthalmitis cases 2007-2014	Penetrating keratoplasty (N=37)	Endothelial keratoplasty (N=60)	Keratoprosthesis (N=1)
Mean incidence per 10,000 grafts	1.8	3.6	6.1

FIGURE 3. Incidence (per 10,000 grafts performed in the United States) of postkeratoplasty endophthalmitis relative to the procedure type, from 2007 to 2014.

Control and Prevention was that none of these systemic infections were definitively because of the donor tissue. In 2010, the 2 tissue recipient cases reported included 1 of *Herpes simplex* encephalitis in a patient who underwent ALK and 1 of HIV in a patient who underwent PK. In 2011 a case of sporadic CJD was reported in a 72-year-old patient that underwent EK.

Donor corneal dystrophy or degeneration was reported in 2 cases that developed keratoconus: (1) in 2007, a case of definite transmission of keratoconus after PK for prior graft failure, from a donor with a history of keratoconus; (2) in 2014, a case of possible transmission of keratoconus after ALK for keratoconus. Although recurrence of the original disease is a plausible explanation, transmission of disease was determined to be likely because of the early presentation and severe clinical course.

Donor corneal refractive surgery was reported in 2 cases in 2013. Both cases underwent successful PK, and the mate tissue was healthy. Scleral graft infection was associated with gram-positive bacilli in 1 case in 2013. Iritis was reported in a single case that underwent PK in 2012. The rim culture was negative, and the mate tissue developed endophthalmitis.

Residual stromal edema after keratoplasty, not consistent with PGF, was reported in a single case that underwent EK in 2014. The tissue was precut using a microkeratome at the eye bank.

DISCUSSION

The importance of reporting adverse reactions relates to improving our practice patterns, ensuring that the field of tissue transplantation learns from these cases, and to potentially change practices to prevent their recurrence. Identifying trends may illustrate public health concerns and may lead to policy changes. An example of this includes the increasing trend in the incidence of post-keratoplasty fungal infections observed in our report. Subsequent policy changes that may

TABLE 3. Spectrum of Organisms Isolated in Endophthalmitis Cases 2007 to 2014*

Genus of Isolate	Number (% of Culture-Positive Cases)	Species	Number (% of Culture-Positive Cases)
Fungus/yeast	53 (65)	*Candida* species	53 (65)
Gram positive	27 (33)	*Enterococcus* species	11 (13)
		Streptococcus species	9 (11)
		Staphylococcus species	4 (5)
		Clostridium perfringens	2 (2)
		Gram-positive cocci	1 (1)
		Hemophilus influenza	1 (1)
Gram negative	2 (2)	*Achromobacter* species	1 (1)
		Escherichia coli species	1 (1)
	Total = 82 isolates		Total = 82 isolates

*Of the 99 endophthalmitis cases, culture was positive in 77 cases, no growth observed in 10 cases, culture not performed in 10 cases, and unable to obtain follow-up information from surgeon in 2 cases.

be considered in light of this trend may include the following: (1) to consider supplementing corneal tissue preservation medium with an antifungal agent and (2) to communicate with corneal transplant surgeons regarding the potential benefit of submitting donor rims for fungal culture at the time of surgery. Although there is inconsistent consensus regarding the clinical utility of a positive bacterial rim culture result and risk of bacterial endophthalmitis,[13,14] it is recognized that there is higher correlation between post-keratoplasty fungal infection and positive rim culture result.[15,16] Despite this, a 2013 EBAA survey reported that only 29% of respondents were performing routine donor rim cultures (Aldave, Anthony. The Utility of Donor Corneal Rim Cultures: A Report of the EBAA Medical Advisory Board Subcommittee on Fungal Infection Following Corneal Transplantation. EBAA/Cornea Society Educational Symposium, November 2015. Las Vegas, NV).

Primary Graft Failure

Published incidence data for post-keratoplasty PGF vary according to the procedure type. Large cohort studies and registry data report the incidence post-PK to range between 0% and 12%.[1–4] The Cornea Donor Study, which evaluated the effect of donor age on the success of PK, reported a PGF incidence of 0.27% (n = 3) from their cohort of 1090 cases.[3] An epidemiologic study from the Veneto Eye Bank Foundation in Italy reported a PGF incidence of 5.6% (n = 6) from 998 grafts used for PK.[1] Studies using Australian graft registry data report the PGF incidence after PK to range between 0.6% and 0.85% (n = 36 of 6031 grafts and n = 41 of 4834 grafts, respectively).[2,4] Comparatively, PGF incidence after PK in our study was significantly lower, at 0.069% (n = 135) of 195,859 grafts.

The incidence of PGF after Descemet stripping endothelial keratoplasty has been reported to range between 0% and 29% (mean 5%) in a 2009 report by the American Academy of Ophthalmology regarding EK safety and outcomes.[17] The data from this report were a synopsis of the peer-reviewed literature and included 34 relevant articles. Comparatively, PGF incidence post-EK in our study was lower, at 0.11% (n = 180) of 164,563 grafts.

There are few reports comparing the incidence of PGF post-PK versus post-EK. One such study including a large cohort of 20,431 tissues distributed from Eversight (formerly the Midwest Eye Banks) reported a PGF incidence of 0.17% (n = 23 of 13,597) after PK and 0.60% (n = 41 of 6834) after EK.[18] Data reported from the Singapore Corneal Transplant Study similarly showed a higher PGF rate of 1.5% after EK (n = 1 of 68 grafts) versus 0.5% after PK (n = 1 of 173 grafts).[19] Similarly, our study showed a higher PGF rate post-EK versus post-PK (0.11% vs. 0.069%).

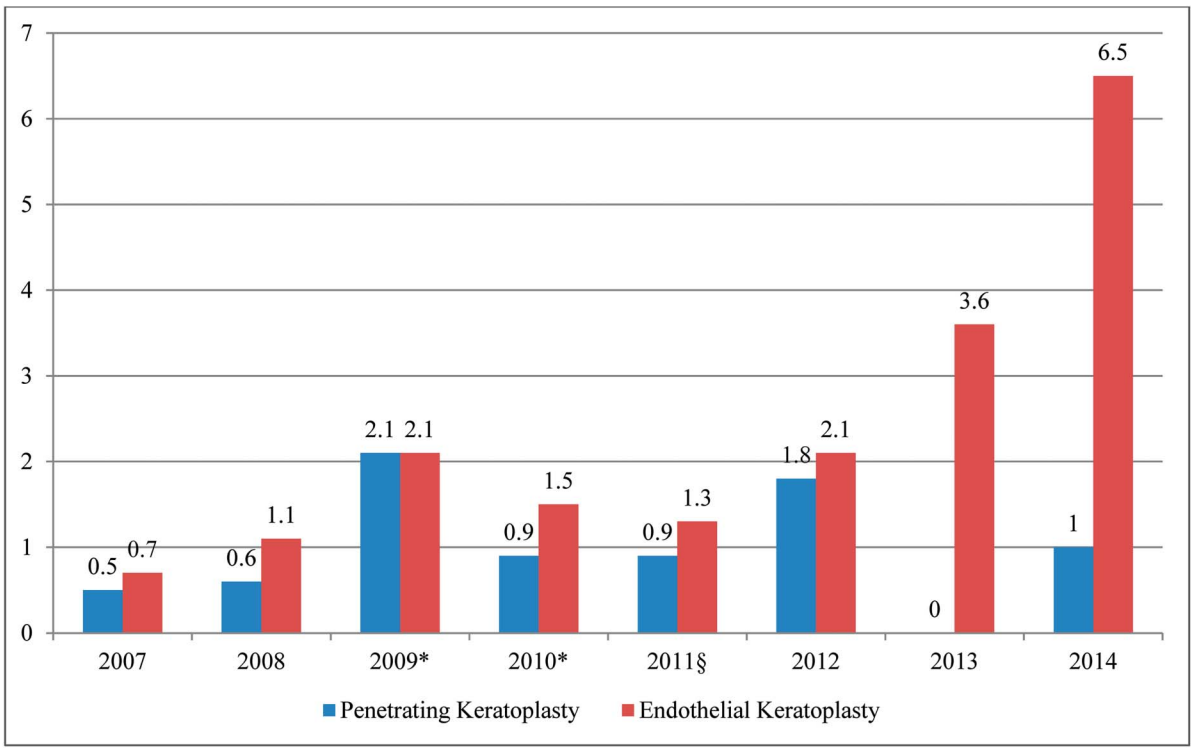
The reason for a higher PGF incidence noted with EK compared with PK is likely multifactorial. There may be inconsistent understanding of the definition of PGF and overreporting as a result. Specifically, PGF is a graft that has not cleared 8 weeks after keratoplasty, is presumed to have occurred because of primary corneal endothelial failure, and is not iatrogenic because of excessive damage incurred during the surgical procedure. Learning curve and surgeon skill factors in to this, as EK has become more widely adopted. Overreporting occurs when these iatrogenic cases are included in the data. It is conceivable that our data from the OARSS report is more likely to have weeded out these iatrogenic cases because of the multiple checks in place to ensure accurate reporting. Specifically, tissue imputability is closely scrutinized by the distributing eye bank, the medical director, and the EBAA medical review subcommittee. This may explain our lower PGF incidence data compared with the published literature.

In addition, reporting is voluntary and at the discretion of the transplant surgeon. Medical standards require that the distributing eye bank send a post-keratoplasty outcome request to the surgeon, but do not necessarily require a documented response, which may lead to underreporting.

Endophthalmitis

The majority of publications reporting the incidence of postkeratoplasty endophthalmitis refer to PK, with less incidence data available relative to EK. The reported incidence of endophthalmitis, which has been generally derived from individual institutions, international registry data, and Medicare databases, ranges from 0.142% to 0.67%.[5–10]

EBAA data published by Hassan et al[8] reported 162 cases of endophthalmitis after PK from 1994 to 2003. The incidence was 0.047% (n = 162) of 340,174 grafts performed in the United States. In comparison, our study had a lower endophthalmitis incidence of 0.018% (n = 37) of 195,859



* In 2009 and 2010 there were two cases of anterior lamellar keratoplasty-related keratitis.
§ In 2011 there was a single case of KPro-related keratitis.

Keratitis cases 2007-2014	Penetrating keratoplasty (N=19)	Endothelial keratoplasty (N=44)	Keratoprosthesis (N=1)	Anterior lamellar keratoplasty (N=2)
Mean incidence per 10,000 grafts	0.9	2.6	6.1	2.6

FIGURE 4. Incidence (per 10,000 grafts performed in the United States) of postkeratoplasty infectious keratitis relative to the procedure type, from 2007 to 2014.

grafts for PK and 0.028% (n = 99) of 354,930 grafts for all corneal transplant types combined. Du et al[7] conducted a Medicare database review from 2006 to 2011 of postkeratoplasty endophthalmitis cases diagnosed within 6 weeks of surgery (based on International Classification of Diseases, 9th revision) and reported an incidence of 0.42% (n = 76) from 18,083 corneal transplants, in comparison with the incidence after cataract surgery of 0.127% (n = 2874) from 2,261,779 cases.

A study including a large cohort of 11,320 transplant recipients published using the UK transplant registry between 1999 and 2006 reported an endophthalmitis incidence of 0.67% (n = 76) after primary PK.[6] A retrospective review of endophthalmitis cases between 1990 and 2007 from the King Khaled Eye Specialist Hospital in Saudi Arabia reported an incidence of 0.61% (n = 46) of 7488 corneal transplants, including penetrating and lamellar keratoplasties.[5]

A study from Emory University in Atlanta including 1010 consecutive penetrating keratoplasties reported an endophthalmitis incidence of 0.39% (n = 4).[9] Taban et al[10] reviewed published data between 1972 and 2002 of endophthalmitis cases after PK and noted an incidence of 0.382% from 90,549 grafts. They also observed a decreasing incidence of endophthalmitis cases after 1992, compared with 1991 and earlier. However, our report reveals an increasing trend of endophthalmitis cases reported over the past several years (Fig. 2), seemingly because of increased fungal pathogens.

Fungal Infections

The reported incidence of fungal infection is approximately 0.033% to 0.16% after corneal transplant.[7,9,20] The incidence of fungal infection including keratitis and endophthalmitis after PK was reported to be 0.16% (n = 4) of 2466 grafts, from the New York Eye and Ear Infirmary.[20] Our study similarly shows low combined fungal infection incidence after keratoplasty at 0.023% (n = 83) of 354,930 grafts.

Review of the literature suggests that bacterial endophthalmitis after PK is more common than fungal etiology. The report by Hassan et al[8] using EBAA data from 1994 to 2003 noted a predominance of bacterial infection in 67% (n = 81) versus fungal infection in 33% (n = 40) of the

TABLE 4. Spectrum of Organisms Isolated in Infectious Keratitis Cases, 2007 to 2014*

Genus of Isolate	Number (% of Culture-Positive Cases)	Species	Number (% of Culture-Positive Cases)
Fungus/yeast	34 (81)	*Candida* species	34 (81)
Herpes virus	3 (7)	*Herpes simplex* virus	3 (7)
Gram positive	2 (5)	*Mycobacterium chelonae*	1 (2)
		Staphylococcus species	1 (2)
Gram negative	3 (7)	*Achromobacter* species	1 (2)
		Escherichia coli	1 (2)
		Pseudomonas aeruginosa	1 (2)
	Total = 42 isolates		Total = 42 isolates

*Of the 66 infectious keratitis cases, culture was positive in 42 cases, not performed in 15 cases, no growth observed in 8 cases, and unable to obtain follow-up information from surgeon in 1 case.

121 culture-positive cases. The report by Chen et al[6] using the UK registry data noted a predominance of bacterial infection in 69% (n = 9) versus fungal infection in 31% (n = 4) of culture-positive cases. Kloess et al[9] from Emory also noted bacterial predominance in 75% (n = 3) versus a single case of fungal endophthalmitis. Alharbi et al[5] from the King Khaled Eye Specialist Hospital in Saudi Arabia noted bacterial predominance in 96% (n = 44) versus fungal infection in 4% (n = 2) of culture-positive endophthalmitis cases. The report by Du et al[7] based on a review of Medicare databases from 2006 to 2011 noted bacterial predominance in 92% (n = 70) versus fungal infection in 8% (n = 6) of cases.

In contrast, our study reveals a reversal of this trend, with a predominance of fungal infection in 65% (n = 53) versus bacterial infection in 35% (n = 29), of the 77 culture-positive cases. Of note, our endophthalmitis cases include those after both PK and EK.

Possible reasons for the relative increased incidence of fungal causative pathogens include the following: (1) To date, there is no routine use of an antifungal agent to supplement corneal storage medium in the United States. (2) A noncompetitive environment is created by increased broad-spectrum antibiotic use killing off bacteria, thus allowing fungi to flourish. (3) The increased warming period time associated with preparing EK tissue in the eye bank has been shown to correlate with increased fungal organism proliferation (Tu, Elmer. The Effect of Repeated Warming Cycles of Corneal Storage Media on Fungal Infection Risk in Endothelial Keratoplasty. EBAA/Cornea Society Educational Symposium, November 2015. Las Vegas, NV). Conversely, the antibacterial activity of Optisol-GS is enhanced at room temperature, thus creating a noncompetitive environment allowing fungi to grow.[21] Reports suggest a high association between fungal infection and EK and tissue prepared in the eye bank, as compared with surgeon-prepared tissue.[15]

Donor-to-host transmission of infection or malignancy is a rare but important consideration associated with corneal transplantation.[22] Possible underreporting may result from difficulty in confirming causative role of systemic transmission and the very long latency period of conditions, such as CJD and HIV. In our study, none of the 3 reported systemic infections were definitively confirmed to be because of the donor tissue. Maddox et al[23] reported the incidence of sporadic CJD cases unrelated to donor tissue, based on a review of 4 cases over a 16-year period, to occur in 1 case every 1.5 years.

Of note, only *probable* and *definite* graft-transmitted adverse reactions were considered reportable categories up until the end of 2013. The EBAA Medical Standard has since been modified so as to harmonize adverse reporting categories with the European SOHO V&S (Vigilance and Surveillance of Substances of Human Origin) categories. The current medical standard defines *possible*, *likely/probable*, and *definite/certain* as reportable adverse reaction categories. A limitation of this study is that donor factor analysis was limited because OARRS only contains donor characteristics data for cases with adverse reactions. Future study comparing unaffected and affected cases should examine whether any donor factors (eg, cause of death, donor on ventilator) are associated with these adverse reactions.

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REFERENCES

1. Fasolo A, Capuzzo C, Fornea M, et al. Risk factors for graft failure after penetrating keratoplasty: 5-year follow-up from the corneal transplant epidemiological study. *Cornea*. 2011;30:1328–1335.
2. Williams KA, Muehlberg SM, Lewis RF, et al. How successful is corneal transplantation? A report from the Australian Corneal Graft Register. *Eye (Lond)*. 1995;9(Pt 2):219–227.
3. Mannis MJ, Holland EJ, Gal RL, et al. The effect of donor age on penetrating keratoplasty for endothelial disease: graft survival after 10 years in the Cornea Donor Study. *Ophthalmology*. 2013;120:2419–2427.
4. Kelly TL, Williams KA, Coster DJ. Corneal transplantation for keratoconus: a registry study. *Arch Ophthalmol*. 2011;129:691–697.
5. Alharbi SS, Alrajhi A, Alkahtani E. Endophthalmitis following keratoplasty: incidence, microbial profile, visual and structural outcomes. *Ocul Immunol Inflamm*. 2014;22:218–223.
6. Chen JY, Jones MN, Srinivasan S, et al. Endophthalmitis after penetrating keratoplasty. *Ophthalmology*. 2015;122:25–30.
7. Du DT, Wagoner A, Barone SB, et al. Incidence of endophthalmitis after corneal transplant or cataract surgery in a medicare population. *Ophthalmology*. 2014;121:290–298.
8. Hassan SS, Wilhelmus KR, Dahl P, et al. Infectious disease risk factors of corneal graft donors. *Arch Ophthalmol*. 2008;126:235–239.
9. Kloess PM, Stulting RD, Waring GO III, et al. Bacterial and fungal endophthalmitis after penetrating keratoplasty. *Am J Ophthalmol*. 1993;115:309–316.
10. Taban M, Behrens A, Newcomb RL, et al. Incidence of acute endophthalmitis following penetrating keratoplasty: a systematic review. *Arch Ophthalmol*. 2005;123:605–609.
11. Eye Bank Association of America. *2014 Eye Banking Statistical Report*. Washington, DC: Eye Bank Association of America; 2015.

12. Food and Drug Administration. *Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps)*. August 2007. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf. Accessed December 12, 2015.
13. Everts RJ, Fowler WC, Chang DH, et al. Corneoscleral rim cultures: lack of utility and implications for clinical decision-making and infection prevention in the care of patients undergoing corneal transplantation. *Cornea*. 2001;20:586–589.
14. Cameron JA, Badr IA, Miguel Risco J, et al. Endophthalmitis cluster from contaminated donor corneas following penetrating keratoplasty. *Can J Ophthalmol.* 1998;33:8–13.
15. Aldave AJ, DeMatteo J, Glasser DB, et al. Report of the Eye Bank Association of America medical advisory board subcommittee on fungal infection after corneal transplantation. *Cornea*. 2013;32:149–154.
16. Wilhelmus KR, Hassan SS. The prognostic role of donor corneoscleral rim cultures in corneal transplantation. *Ophthalmology*. 2007;114:440–445.
17. Lee WB, Jacobs DS, Musch DC, et al. Descemet's stripping endothelial keratoplasty: safety and outcomes: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2009;116:1818–1830.
18. Ple-plakon PA, Shtein RM, Musch DC, et al. Tissue characteristics and reported adverse events after corneal transplantation. *Cornea*. 2013;32:1339–1343.
19. Ang M, Mehta JS, Anshu A, et al. Endothelial cell counts after Descemet's stripping automated endothelial keratoplasty versus penetrating keratoplasty in Asian eyes. *Clin Ophthalmol.* 2012;6:537–544.
20. Keyhani K, Seedor JA, Shah MK, et al. The incidence of fungal keratitis and endophthalmitis following penetrating keratoplasty. *Cornea*. 2005;24:288–291.
21. Kapur R, Tu EY, Pendland SL, et al. The effect of temperature on the antimicrobial activity of Optisol-GS. *Cornea*. 2006;25:319–324.
22. Dubord PJ, Evans GD, Macsai MS, et al. Eye banking and corneal transplantation communicable adverse incidents: current status and project NOTIFY. *Cornea*. 2013;32:1155–1166.
23. Maddox RA, Belay ED, Curns AT, et al. Creutzfeldt-Jakob disease in recipients of corneal transplants. *Cornea*. 2008;27:851–854.