An Outbreak of *Fusarium* Keratitis Associated With Contact Lens Use in the Northeastern United States

Jason J. Gorscak, MD, Brandon D. Ayres, MD,† Neelakshi Bhagat, MD,* Kristin M. Hammersmith, MD,† Christopher J. Rapuano, MD,† Elisabeth J. Cohen, MD,† Michele Burday, PhD,‡ Neena Mirani, MD,‡ Donald Jungkind, PhD,§ and David S. Chu, MD**

Purpose: To report an outbreak of *Fusarium* keratitis in contact lens (CL) wearers in the northeastern United States.

Methods: Over a 41-month period, all cases with culture-proven corneal ulceration secondary to *Fusarium* at 2 tertiary care eye centers were identified through the microbiology departments of each institution, and a retrospective review of charts was performed. Statistical analyses were performed to evaluate a possible association of *Fusarium* keratitis with specific CL and CL solution brands.

Results: Fifteen cases of *Fusarium* keratitis were reported at the 2 tertiary centers between July 2005 and May 2006 (16.4 cases/yr) compared with 6 cases over the previous 30 months from January 2003 to June 2005 (2.4 cases/yr). All 15 of the more recent cases were CL users, and none had a history of trauma. All 15 patients claimed use of ReNu brand contact lens solution when they developed keratitis. Twelve (80.0%) of 15 patients were Acuvue soft contact lens users. Ten (66.7%) of 15 patients used tap water to rinse their contact lens cases. Six (40.0%) of 15 cases have thus far required corneal transplantation.

Conclusions: The incidence of corneal ulceration secondary to *Fusarium* has increased sevenfold over the reported 11-month period at 2 tertiary eye care centers in the northeastern United States compared with the previous 30 months. There seems to be an association between the recent outbreak of *Fusarium* keratitis among CL users and the use of ReNu contact lens solution. Medical treatment of *Fusarium* keratitis may be ineffective, and emergent penetrating keratoplasty (PKP) may be required in some patients. CL users and their physicians should reconsider the risks of CL use and discuss proper lens care techniques.

Key Words: *Fusarium*, keratitis, fungus, contact lens

(*Cornea* 2007;26:1187–1194)

Received for publication January 9, 2007; revision received June 1, 2007; accepted June 12, 2007.

From the *Institute of Ophthalmology and Visual Science, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ; †Corneal Service, Wills Eye Hospital, Thomas Jefferson College, Thomas Jefferson University, Philadelphia, PA; ‡Pathology and Laboratory Medicine, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ; and §Department of Pathology, Thomas Jefferson University, Philadelphia, PA.

Supported in part by an unrestricted grant from Research to Prevent Blindness.

Reprints: David Chu, Doctors Office Center, 90 Bergen St., Suite 6100, Newark, NJ 07101 (e-mail: chuda@umdnj.edu).

Fungal keratitis is a rarely encountered condition in the northeastern United States. Asbell and Stenson[1] reviewed 30 years of data at New York University Medical Center in the 1980s and found that 1% of all microbial keratitis was caused by fungal etiology. Ritterband et al[2] studied >5000 cases of microbial keratitis at the New York Eye and Ear Infirmary and concluded that only 1.2% of cases were caused by fungi. Fungal keratitis is a condition more prevalent in tropical and subtropical regions.[3] Some studies indicate that up to 35% of microbial keratitis cases are fungal keratitis.[4,5] The proportion of fungal keratitis attributable to *Fusarium* species also varies by region, from 25% to 62%.[4,6,7] *Fusarium* keratitis is most common among agricultural workers in geographical regions with tropical or semitropical climates.[8] *Fusarium* is commonly found in soil, plants, or aqueous environments.[9,10] It is not transmitted from person to person. First-line treatment includes topical and oral antifungal medications. Patients who do not respond to medical treatment usually require surgical intervention such as corneal transplantation.[3]

Approximately 38 million people in the United States wear contact lenses (CLs).[11] The annual incidence of microbial keratitis is estimated to be 4–21 per 10,000 soft CL (SCL) users, depending on the techniques of lens care and use.[12] Risk factors for microbial keratitis include trauma, chronic ocular surface diseases, immunodeficiency, and CL use.[3,6,7,13,14] Additional risk factors for CL wearers include overnight wear, smoking, and possibly poor hygiene habits.[15–17]

An outbreak of *Fusarium* keratitis became evident in the United States during early 2006.[18–21] The *Fusarium* keratitis epidemic was first brought to the public's attention in Singapore in February 2006, which led to the withdrawal of ReNu (Bausch and Lomb, Rochester, NY) contact lens solution from the Singapore and Hong Kong markets at that time.[22–24]

The goal of our study is to inform the medical community of the *Fusarium* keratitis outbreak among SCL wearers and to share our clinical experience with these patients.

MATERIALS AND METHODS

Approval was obtained from the institutional review board offices of the University of Medicine and Dentistry of New Jersey (UMDNJ) Newark Campus, Newark, NJ, and Wills Eye Hospital (WEH) of Thomas Jefferson University Hospital, Philadelphia, PA, for a retrospective study. Cases of culture-proven *Fusarium* keratitis were identified by reviewing

the databanks of the microbiology departments at each institution. Cases occurring between January 1, 2003, and June 30, 2005, were placed in group A, and those identified between July 1, 2005, and May 31, 2006, were placed in group B. Total number of patients with infectious keratitis during the same periods was also identified as historical controls for keratitis by searching the data banks at the Institute of Ophthalmology and Visual Science (IOVS) of New Jersey Medical School and WEH by using ICD-9 codes for infectious keratitis including 370.00 (corneal ulcer, unspecified), 370.01 (corneal ulcer, marginal), 370.02 (corneal ulcer, ring), 370.03 (corneal ulcer, central), and 370.04 (corneal ulcer, hypopyon). This tabulation included all patients with infectious keratitis who were either treated as an outpatient or hospitalized for their condition at each institution. Patients found to have multiple visits for infectious corneal ulcers within a 3-month period had only their initial visit counted while tabulating the data. This group included CL wearers and non-CL wearers and culture-proven and non–culture-proven patients with infectious keratitis.

For subjects in group A, charts were reviewed with attention to any potential risk factors for microbial keratitis. For group B, in addition to risk factors, details of clinical findings and course were examined through March 31, 2007. All patients in group B had culture-proven *Fusarium* keratitis either from culture of corneal scraping, culture from a CL case, or culture from the corneal button.

Data were also obtained by reviewing the questionnaire created by the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, and state health departments with input from some of the authors of this study. The questionnaire was completed during interviews between the patient and a representative from the state health department before initiation of this study.

A case–control study was implemented for group B patients to assess whether CL solution or specific brands of lenses were risk factors for the infection. Cases were identified, as mentioned above, from the databanks at the microbiology department of each institution for culture-proven *Fusarium* keratitis between July 2005 and May 2006. Twice as many controls were identified for each case using ReNu CL solution and for each case using Acuvue contact lenses.

The controls were randomly chosen from a list of patients who were CL wearers seen in the outpatient CL clinic at IOVS between June 2005 and May 2006. The list included only those patients who had purchased CLs from IOVS with no active eye diseases at the time of lens purchase. The controls were all community based, and no inpatients were included. All the controls were chosen from IOVS, and none were from the WEH.

The information about controls was collected from a retrospective review of their clinic chart. The data gathered included the type of CL and any visits to the eye clinics for any corneal ulcer. They were also contacted by phone to confirm the CL solution and CLs they may have used during this period and to find out if they had developed a corneal ulcer that may have been treated elsewhere. Only culture-proven corneal ulcers were included for the diagnosis of *Fusarium* keratitis in both cases and controls.

Controls were randomly selected from this database by using Research Randomizer, which uses an adaptation of the Central Randomizer by Houle.[25] Brands of CLs available to patients through UMDNJ-IOVS included all manufactured by Ciba Vision, Cooper Vision, Johnson & Johnson, and Bausch & Lomb.

Data analysis was carried out by using the 2-way contingency table using Epi Info. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated in the univariate analysis.

RESULTS

Twenty-one cases of culture-proven *Fusarium* keratitis were identified at IOVS and WEH between January 1, 2003, and May 31, 2006 (Fig. 1); 6 cases occurred between January 1, 2003, and June 30, 2005 (group A): 3 at the IOVS and 3 at WEH (Table 1). Of these cases, 5 (83.3%) were diagnosed by culture of corneal scraping and 1 was diagnosed after corneal transplantation and culture of the corneal button. Four (66.7%) of these 6 patients were soft CL wearers, and there was no history of trauma among any of these patients. The brand of CL solution, hygiene habits, and brand of CLs worn by these patients were unknown.

Fifteen (71.4%) of 21 cases presented between July 1, 2005, and May 30, 2006 (group B); 5 were diagnosed and treated at IOVS and 10 at WEH. Of the 15 cases, everyone underwent corneal scraping, some with multiple attempts; as a result, 12 (80.0%) grew *Fusarium* species from the culture of their corneal scraping. One (6.7%) patient showed a positive culture from his CL case of 3 CL cases cultured. One patient had a positive culture from his aqueous humor after anterior chamber paracentesis, and 1 patient was diagnosed from the culture of his corneal button after corneal transplantation. Of the 6 corneal buttons from patients requiring emergent corneal transplantation, 4 (67.7%) grew *Fusarium*. There was no history of immunodeficiency among any of these patients.

In a 30-month period before the outbreak, only 6 cases of *Fusarium* keratitis presented to IOVS and WEH between January 1, 2003, and June 30, 2005 (2.4 cases/yr) compared with 15 cases in the 11-month period between July 1, 2005, and May 31, 2006 (16.4 cases/yr; Fig. 2). This was a sevenfold increase in the number of *Fusarium* keratitis cases at the 2 institutions. During the same period, the total number of

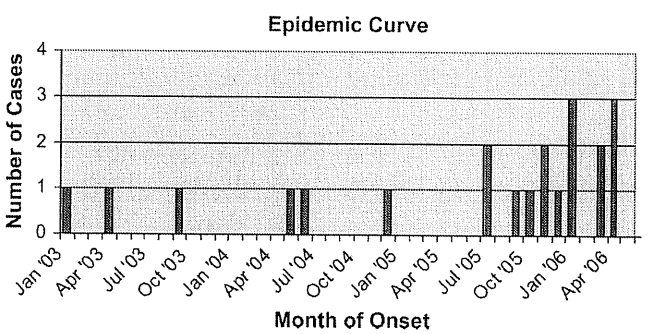

FIGURE 1. Number of cases of *Fusarium* keratitis at the 2 tertiary care centers over a 41-month period.

TABLE 1. Number of Cases by Location During Respective Periods

	January 1, 2003, to June 30, 2005	July 1, 2005, to May 31, 2006
Fusarium keratitis		
IOVS	3	5
WEH	3	10
IOVS + WEH	6 (2.4 cases/y)	15 (16.4 cases/y)
Infectious corneal ulcers		
IOVS	312	133
WEH	917	611
IOVS + WEH	1229 (491.6 cases/y)	744 (811.6 cases/y)

IOVS, The Institute of Ophthalmology and Visual Science; WEH, Wills Eye Hospital; CL, contact lens.

infectious corneal ulcers, regardless of etiology, that presented to IOVS and WEH were 312 and 917 (1229 cases total and 491.6 cases/yr combined), respectively, between January 1, 2003, and June 30 2005; 133 and 611 (744 cases total and 811.6 cases/yr combined), respectively, between July 1, 2005, and May 31, 2006 (Table 1).

The median age of the cases in group B was 44 years, and the mean age was 41.1 years (range, 19–67 years). Six (40.0%) patients had only their right eye involved, whereas 8 (53.3%) patients had only their left eye involved. One (6.7%) patient had simultaneous bilateral disease. Four (26.7%) patients were men, and 11 (73.3%) were women. Two (13.3%) patients reported being in a tropical climate within 1 month before symptom onset, 1 in both Hawaii and Mississippi and the other in Puerto Rico. One (6.7%) patient reported gardening within 1 hour of symptom onset. There was no history of trauma among any of these patients within 1 month before the onset of their symptoms. Our patients seemed to represent a wide range of social backgrounds (Table 2).

All 15 cases in group B were SCL wearers. All 15 cases reported using ReNu contact lens solution to rinse and store their contact lens. Eleven (73.3%) of 15 patients used ReNu with MoistureLoc Solution, whereas 4 (26.7%) of 15 recalled using ReNu Multiplus Multipurpose Solution (Table 3).

Statistical analysis results suggested an association between the use of ReNu contact lens solution and *Fusarium* keratitis from univariate analysis (Table 4). Further detailed analysis using the subtype of ReNu contact lens solution (MoistureLoc versus Multiplus Multipurpose) could not be performed because we could not ascertain the subtype of ReNu contact lens solution in the controls. No patients in the control group had a history of corneal ulceration during the periods analyzed.

Twelve of 15 patients wore a brand of Acuvue lens (Johnson & Johnson, New Brunswick, NJ). Eight (53.3%) of 15 patients used Acuvue 2 contact lens, 2 (13.3%) patients used Acuvue but were unsure of the type, 1 (6.7%) patient used Acuvue Bifocal, and 1 patient used Acuvue Oasis. Of the other 3 patients, 1 patient used O_2Optix (Ciba Vision, Duluth, GA), and 2 (13.3%) patients were unsure of the brand (Table 3). Twenty-six controls were obtained, and the results of the univariable analysis did not suggest an association between

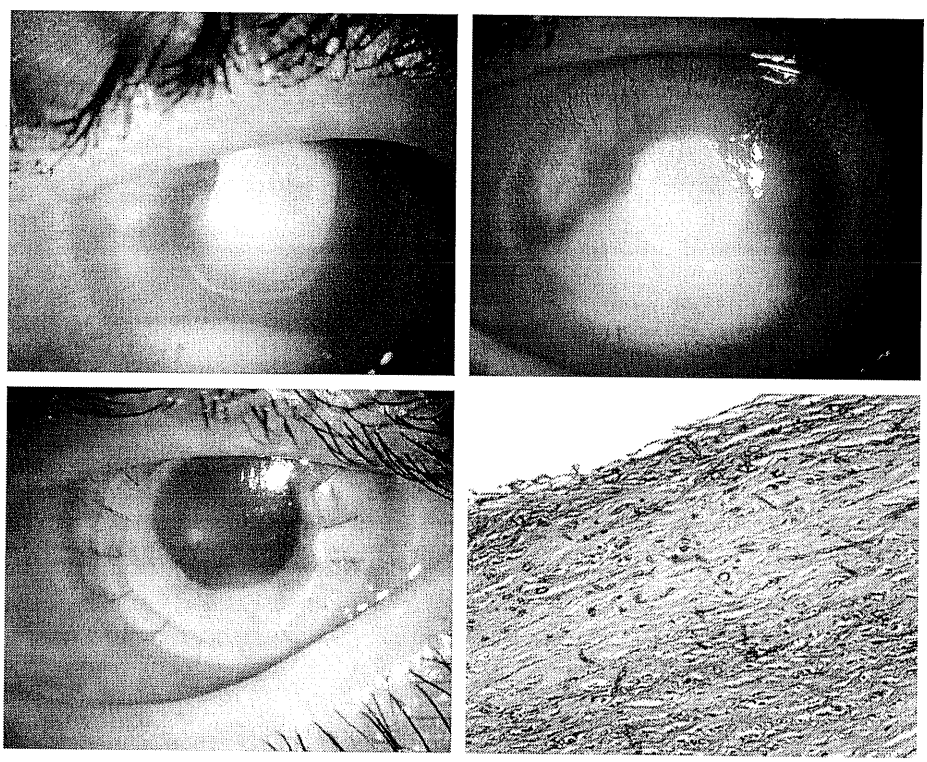

FIGURE 2. *Fusarium* keratitis. Top Left, April 7, 2006, date of presentation; 14 days after onset of symptoms. Top Right, April 13, 2006; 5 days after starting topical voriconazole and natamycin and systemic voriconazole. Bottom Left, April 19, 2006; 1 day after corneal transplantation. Bottom Right, Light microscopy image of the corneal button showing septate fungal hyphae (periodic acid–Schiff stain; magnification, ×400).

TABLE 2. Demographics of Patients With *Fusarium* Keratitis Between June 2005 and May 2006

Patient No.	Age (y)	Sex	Eye	Hospital	Occupation	Recent Trauma	Recent Travel to Tropical Climate	Date of Symptom Onset
1	54	Female	OD	WEH	School teacher	No	No	7/1/2005
2	22	Female	OS	WEH	Student	No	No	7/14/2005
3	51	Female	OS	WEH	Waitress	No	No	9/1/2005
4	65	Female	OD	WEH	Bridal salon owner	No	No	10/1/2005
5	67	Female	OD	WEH	Retired teacher	No	No	11/3/2005
6	21	Male	OU	WEH	Student	No	No	11/6/2005
7	44	Female	OS	IOVS	Homemaker	No	No	12/20/2005
8	56	Female	OS	WEH	Secretary	No	No	1/3/2006
9	52	Female	OD	IOVS	Housekeeper	No	No	1/15/2006
10	26	Male	OD	IOVS	Construction	No	Yes	1/31/2006
11	27	Male	OS	WEH	Information technology	No	No	3/6/2006
12	28	Male	OS	IOVS	Mechanic	No	Yes	3/23/2006
13	48	Female	OD	IOVS	Secretary	No	No	4/18/2006
14	37	Female	OS	WEH	Surgical coordinator	No	No	4/25/2006
15	19	Female	OS	WEH	Student	No	No	4/28/2006

OD, right eye; OS, left eye; IOVS, Institute of Ophthalmology and Visual Sciences; WEH, Wills Eye Hospital.

infection and the Acuvue brand CLs (OR = 2; 95% CI = 0.381–10.037; Table 4).

CLs and CL case hygiene was different among all of our patients. Three (20%) patients reported always rubbing and rinsing their CLs with CL solution (CLS) before overnight storage, 1 (6.7%) patient occasionally rubbed and rinsed his CLs, 1 patient always rubbed his CLs without rinsing, 1 patient always rinsed his CLs, 1 patient occasionally rinsed his CLs, and 7 patients' habits were unknown. One patient reported never rubbing or rinsing his CLs before overnight storage. All patients reported storing their lenses in CL solution overnight. Patients reported different methods for rinsing their CL case. Ten (66.7%) of 15 patients used tap water, 3 (20.0%) patients used CL solution only, and 2 (13.3%) patients used both CL solution and tap water intermittently. Nine (60.0%) of 15 patients reported changing their CL case every 3 months or less, 4 (26.7%) patients every 3–6 months, and 1 (6.7%) patient approximately every year. One patient did not know how old his CL case was. Eight (53.3%) of 15 patients reported that their CL solution was <6 months old, 1 (6.7%) patient stated it was >6 months old, and 6 (40.0%) patients could not comment on how old their solution was. Two patients reported consistently sleeping in their contact lenses up to 3–4 times per week; all other patients reported removing their SCLs each night (Table 3). In addition, the questionnaire asked for patients' handwashing habits and CL replacement frequency,

TABLE 3. Contact Lens Solution, Lens, and Hygiene Demographics

Patient No.	Type of ReNu	Brand of CL	Storage Solution for CL	Age of CL Solution (mo)	Age of CL Case (mo)	Method of CL Case Rinse	Sleep in CL (nights/wk)
1	ML	Acuvue	CLS	3	6	CLS + TW	No
2	MP	Acuvue 2	CLS	Unknown	6	TW	No
3	ML	Acuvue	CLS	4	3	TW	No
4	ML	Unknown	CLS	1	1	CLS + TW	No
5	MP	Acuvue Bifocals	CLS	Unknown	Unknown	TW	No
6	ML	Acuvue 2	CLS	2	Unknown	TW	Yes (3)
7	ML	Acuvue 2	CLS	Unknown	<3	TW	No
8	ML	Acuvue 2	CLS	3	2	CLS	No
9	MP	Unknown	CLS	Unknown	Years	TW	No
10	ML	Acuvue Oasys	CLS	3	<3	CLS	No
11	MP	Acuvue 2	CLS	2	6	CLS	No
12	ML	Acuvue 2	CLS	2	2	TW	Yes (4)
13	ML	O_2Optix	CLS	6	1	TW	No
14	ML	Acuvue 2	CLS	Unknown	2	TW	No
15	ML	Acuvue 2	CLS	Unknown	2	TW	No

CL, contact lens; Y, yes; N, no; CLS, contact lens solution; ML, MoistureLoc; MP, Multiplus Multipurpose; TW, tap water.

TABLE 4. Association Between *Fusarium* Keratitis and Exposure in CL Solution Outbreak, June 2006: Main Results of Unmatched Univariable Analysis

Exposure	No. Cases Exposed	No. Controls Exposed	OR	95% CI
ReNu CL solution	15/15	18/30	Infinite*	Interval does not include 1
Acuvue	12/14	18/24	2	0.381–10.037

*Because all cases were on ReNu; "0" cases on CL solution other than ReNu (please refer to details in the Discussion section).

CL, contact lens; OR, odds ratio; CI, confidence interval.

but only a minority of the patients replied to these questions; therefore, the data are not presented.

Of the patients in the study, 13 (86.7%) of 15 patients had taken a topical antibiotic before diagnosis, 6 (40.0%) of 15 had taken a topical or oral steroid, 6 (40%) of 15 had taken either a topical or oral antiviral, and 5 (33.3%) of 15 had taken a topical antifungal before a culture-proven diagnosis was made (Table 5).

Twelve (80.0%) of 15 patients had medical treatment consisting of 1 or more topical antifungal drops (amphotericin B 0.15%/natamycin 5%/voriconazole 1%) used every hour in combination with an antifungal agent given systemically. One patient in this subset received voriconazole intravenously. Two (13.3%) patients were managed with topical antifungal medications only, and 1 (6.7%) patient's treatment regimen was unknown. Two (13.3%) patients received anterior-chamber injections of 0.1 mL of 5 μg/0.1 mL amphotericin B, and 1 (6.7%) patient received 0.1 mL of 1 μg/0.1 mL voriconazole intrastromally. All 3 of these patients who received either intrastromal or intraocular injection of antifungal medication ultimately required subsequent emergent corneal transplantation (Table 6). Of note, 1 patient's treatment was unknown because the patient was referred to WEH for diagnosis only; once diagnosis was established, treatment was initiated by the patient's outside ophthalmologist.

Thus far, 6 (40.0%) of 15 patients have required emergent corneal transplantation to control infection. The preoperative best-corrected visual acuity (BCVA) in all 6 patients was hand motion as determined by pinhole. Of these 6 cases, 2 had undergone subsequent cataract extraction with intraocular lens implantation, 1 had pars plana vitrectomy for endophthalmitis with subsequent repeat penetrating keratoplasty (PKP) for graft rejection, and 2 cases underwent repeat PKP for graft rejection. One of these cases requiring repeat PKP had concurrent extracapsular cataract extraction and trabeculectomy at the time of repeat PKP; subsequently, this case also required a shunting procedure for failure of the trabeculectomy (Table 6).

The average postoperative BCVA was measured with reference to the patient's most recent ocular surgery. With this, BCVA was measured at an average of 5.6 ± 4.0 months. Both (33.3%) patients who had their most recent BCVA measured within 3 months postoperatively were 20/400. One (16.7%) patient examined just over 3 months postoperatively had a BCVA of 20/60. This patient reported a history of amblyopia without knowledge of her visual acuity before corneal ulceration. Of the patients who were examined between 6 and 12 months postoperatively, 1 patient had a BCVA of

TABLE 5. Medical Therapy Used Before Diagnosis

Patient	Medications			
	Antibacterial	Antifungal	Antiviral	Steroidal
1	C, TO	None	None	None
2	Unknown	Unknown	Unknown	Unknown
3	TO, C, GE	AM	Yes*	PR
4	M	N	T, V	L
5	G, VA, TO, O	Yes*	None	None
6	G	None	V	None
7	VA, G, B	AM, VO	A	P
8	M	None	None	None
9	TO, G	AM	T	P, D
10	M	None	None	None
11	M, G	None	A, T	L, P
12	E	None	None	None
13	TO, M	None	None	D
14	none	None	None	None
15	M	None	None	None

*Name of drug unknown.

A, oral acyclovir; AM, topical amphotericin B 1%; B, topical bacitracin; C, topical cefazolin; D, topical dexamethasone; E, opical erythromycin; G, topical gatifloxacin; GE, topical gentamicin; L, topical loteprednol; M, topical moxifloxacin; N, topical natamycin 5%; O, topical ofloxacin; P, topical prednisolone; PR, oral prednisone; T, topical trifluridine; TO, topical tobramycin; V, oral valacyclovir; VA, topical vancomycin; VO, oral voriconazole.

TABLE 6. Medical and Surgical Therapy of *Fusarium* Keratitis

Patient	Medications	Corneal Transplant	Other Intraocular Surgery
1	N	Unknown*	Unknown*
2	Unknown	Unknown*	Unknown*
3	N, VR, VO	Yes	RPKP, ECCE, TRAB, GLTSH
4	N, VR, VO	No	No
5	AM, VR, VO	No	No
6	VR	No	No
7	N, VO, AAC	Yes	No
8	VR, VO	Yes	CEIOL
9	N, VO, F, AAC	Yes	CEIOL
10	N, VR, VO	No	No
11	N, I	No	No
12	N, VR, VO, VIV, VIS	Yes	RPKP
13	AM, VR, VO	Yes	PPV, RPKP
14	N, VO	No	No
15	N, VO	No	No

*Patient seen in consultation only without follow-up.

N, topical natamycin 5%; VR, topical voriconazole 1%; AM, topical amphotericin B 1%; VO, oral voriconazole; VIV, voriconazole intravenously; F, oral fluconazole; I, oral itraconazole; AAC, amphotericin anterior-chamber injection; VIS, voriconazole intrastromal injection; RPKP, repeat penetrating keratoplasty; ECCE, extracapsular cataract extraction; TRAB, trabeculectomy; GLTSH, glaucoma tube shunt; CEIOL, cataract extraction with intraocular lens implantation; PPV, pars plana vitrectomy.

20/20 and 1 was count fingers. Finally, 1 patient examined >12 months postoperatively was 20/25 (Table 7).

Of the 10 eyes in 9 patients who were treated medically in our clinics, the BCVA was measured at an average of 4.6 ± 3.7 months from their first visit. Six patients had a most recent BCVA between 20/20 and 20/40 and 2 between 20/50 and 20/100. Two patients were seen in consultation for diagnostic purposes only and followed up with their outside eye care professional. When BCVA was measured within 3 months of medical treatment, 3 patients had BCVA between 20/20 and 20/40 and 2 patients between 20/50 and 20/100. One patient treated between 3 and 6 months had a BCVA of 20/20, 1 patient treated between 6 and 12 months had a BCVA of 20/25, and 1 patient treated >12 months had a BCVA of 20/20 (Table 6).

DISCUSSION

In February 2006, officials in Singapore and Hong Kong reported an increased incidence of *Fusarium* keratitis among CL wearers in Asia.[16,22,23] Shortly thereafter, more *Fusarium* keratitis cases was noted among CL wearers and brought to the public's attention in the United States.[18–21] Our review confirms that the incidence of corneal ulceration secondary to *Fusarium* has increased sevenfold over the reported 11-month period at 2 tertiary eye care centers in the northeastern United States compared with the previous 30 months. Although the exact events that precipitated this outbreak are yet to be determined, studies are under way at federal institutions and at various centers internationally.[18,22] In the latest outbreak, use of Bausch & Lomb's ReNu with MoistureLoc Solution was identified as a common element in most cases.[16,19,21] On May 15, 2006, Bausch & Lomb announced a permanent global recall of this solution.

We reviewed the incidence and characteristics of *Fusarium* keratitis at our centers in the northeast over 11 months and compared these cases with those that presented in the previous 30 months. The incidence of *Fusarium* keratitis cases increased sevenfold, from 2.4 (between January 1, 2003, and June 30, 2005) to 16.4 cases/yr (between July 1, 2005, and May 31, 2006); however, during the same period, the incidence of infectious corneal ulcers at the 2 institutions increased only 1.6-fold, from 491.6 to 811.6 cases/yr. All cases of *Fusarium* keratitis identified by our study were culture proven. The diagnostic technique had not changed during the 2 compared periods in identifying this fungal organism. Using ICD-9 codes to identify the cases of infectious corneal ulcers has its limitations. Both sensitivity and specificity were probably reduced in this method; however, it provides an estimate, which serves its purpose in our comparison.

Our study suggests an association between *Fusarium* keratitis among CL users and the use of ReNu contact lens solution. All 15 patients with culture-proven *Fusarium* keratitis in the last 11 months at the 2 institutions were using ReNu contact lens solution; 11 of 15 cases were using ReNu MoistureLoc Solution and 4 used ReNu Multiplus Multipurpose Solution. This outbreak analysis has several limitations, however. The OR analysis had to be approximated because all of the cases were of patients that used ReNu contact lens solution. A direct calculation revealed OR to be infinite because "0" was used for 1 of the cells in the 2 × 2 contingency table (0 numerical value for those cases that used other CL solutions besides ReNu). Two separate analyses were performed by using the numerical values 0.1 and 0.5 in the 2 × 2 table cell instead of 0. For a value of 0.5, the OR was 20 (95% CI, 1.795–208.063); for a value of 0.1, the OR was 100 (95% CI, 2.243–4118.287). As the value approaches 0 in the cell, the OR approaches infinity, and the 95% CI moves in a direction away from 1.0, suggesting a statistically significant association between *Fusarium* keratitis and the use of ReNu contact lens solution.

In 2002, Johnson & Johnson, the maker of Acuvue contact lenses, had the largest market share for CLs in the United States at 36%.[26] A much larger proportion of patients who developed *Fusarium* keratitis were wearing Acuvue contact lenses than any other brand. However, our analysis did not find an association between *Fusarium* keratitis and Acuvue CL wear.

In this study, all the controls were chosen from IOVS and none from the WEH. A selection bias may exist with these controls because there could be regional differences in the market share of the CLS sale in New Jersey and Pennsylvania. In addition, it is possible that controls may have preferred 1 brand of CLS or CL type depending on the recommendations made by the health care providers at this institution. If the controls were chosen from the community over the 2 states, it could have been more random. Also, because the demographic

TABLE 7. BCVA After Medical or Surgical Treatment

	Medical				Surgical			
BCVA PO	0–3 mo Tx	3–6 mo Tx	6–12 mo Tx	>12 mo Tx	0–3 mo PO	3–6 mo PO	6–12 mo PO	>12 mo
20/20–20/40	3	1	1	1	0	0	1	1
20/50–20/100	2	0	0	0	0	1*	0	0
20/200–20/400	0	0	0	0	2	0	0	0
CF–HM	0	0	0	0	0	0	1	0
LP–NLP	0	0	0	0	0	0	0	0
Total	5	1	1	1	2	1	2	1

Of note, 2 patients did not have follow-up because they were seen in consultation for diagnosis only.
*Eye with history of amblyopia.
BCVA, best-corrected visual acuity; Tx, treatment; PO, postoperatively; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception.

information of the controls was taken from the chart review, we did not have detailed information about the specific subtype of ReNu CLS being used, and subanalysis with the type of CLS could not be undertaken.

Another limitation to our study is that there may be a recall bias in relation to the specific CLS and CL brand that each patient was using. These parameters were determined by reviewing the questionnaires administered by each state's Department of Health. If patients were not completely sure of which CLS or brand they used during the onset of symptoms when answering these questions, this may have altered our statistical analysis. However, all questionnaires were completed before the CDC's initial report in *Morbidity and Mortality Weekly Report* on April 14, 2006.[18]

Because fusariosis is a relatively rare cause of infectious keratitis, there are no clearly defined guidelines for its management. Existing topical and systemic antifungal medications seem inefficient and ineffective at times. Furthermore, topical antifungal medications are typically difficult to obtain. Although there are mixed reports in the literature on the efficacy of voriconazole in the eradication of *Fusarium* species, our preferred medical regimen for the management of *Fusarium* keratitis, in the midst of the outbreak, included the use of 2 topical antifungal medications (natamycin 5% and voriconazole 1%) given every hour in combination with voriconazole 400 mg systemically every 12 hours times 2 doses followed by 200 mg systemically twice daily thereafter.[6,27–32]

The ophthalmic formulation of voriconazole 1% drops is prepared from the lyophilized powder intended for parenteral administration. Our finding that one third of treated patients required surgical intervention despite the above combination of therapy indicates that further studies need to be performed to determine the optimal medication or combination of medications needed to treat *Fusarium* keratitis.

More than one third of patients in group B required emergent corneal transplantation because these patients exhibited progressive worsening of their disease despite maximal medical therapy. These numbers are higher than in previous publications pertaining to this outbreak.[20,21,23] The discrepancy may be caused in part by how microbial keratitis is approached by ophthalmologists in different parts of our country.

Table 6 may be indicative of how ophthalmologists in the northeast treat microbial keratitis before establishing microbiological confirmation. Among our cases, 40% of patients had received steroids compared with only 33.3% receiving antifungal therapy before the etiology was confirmed, suggesting that fungal keratitis was not suspected in most cases. Interestingly, more patients had received antiviral therapy than antifungal therapy (40.0% versus 33.3%) before the causative organism was determined. This outbreak of *Fusarium* keratitis should serve as a reminder to ophthalmologists, in particular those who rarely treat fungal keratitis, to be on the alert for such condition. It should also remind us that culture is a vital part of the management algorithm for corneal ulcers. Physicians should also reevaluate their approach to and selection of therapy for microbial keratitis of uncertain etiology.

The use of corticosteroids in the setting of fungal keratitis is controversial. Schreiber et al[33] showed that certain cases of fungal keratitis treated with fluconazole plus adjunct high-dose prednisolone treatment administered 9 days after infection may have beneficial effects on outcome. Other studies by Kaufman[34] and Stern and Buttross[35] clearly showed a negative effect of corticosteroids in the treatment of fungal keratitis. O'Day et al[36] showed, in rabbits, that the microbial count of fungal organisms in fungal keratitis remained constant for a longer period with combined therapy with antifungals and corticosteroids than with those corneas treated with antifungals alone. The use of a steroid in the absence of a simultaneous antifungal medication can exacerbate these infections, making them more difficult to treat.[33,35,37]

In addition to the requirement for a better treatment of *Fusarium* keratitis, more sensitive tests for diagnosing this disease are also needed. The most common way to culture a corneal ulcer is through corneal scraping. Among our patients, one fifth of patients had an inconclusive diagnosis from fungal culture of their corneal scraping. Furthermore, at times, it took up to 3 weeks to grow *Fusarium* species on the culture media, and in the same cases, multiple corneal scrapings were required, delaying diagnosis and proper medical management. Polymerase chain reaction and confocal microscopy may be a more sensitive and rapid way to make the diagnosis of *Fusarium* keratitis when it is clinically suspected.[38–40] Given the current outbreak, these protocols should be further evaluated in patients with risk factors for *Fusarium* keratitis.

It is important for a CL wearer to care for and clean his CLs and case properly.[12,13] Among those patients with *Fusarium* keratitis, the CL care routine and habits varied greatly. All patients stored their CLs in CLS; however, 12 of 15 of our patients reported using tap water to rinse their CL case on a regular basis. There have been multiple publications analyzing whether or not *Fusarium* species may be found in ordinary tap water[9,10,41,42]; the results of these publications are varied. Nevertheless, rinsing CL cases with homemade saline, expired CLS, or tap water is not considered by most ophthalmologists to be an appropriate cleansing practice, because of the possible risk of contaminating the CL care system with *Fusarium* and the risk of contracting *Acanthamoeba* keratitis.[2,43,44] We examined the instructions on the boxes of several different multipurpose CLSs from different manufacturers and determined that, at times, the instructions on proper hygiene were unclear and lacked specific details. Furthermore, because telephone and Internet purchasing of CLs has become more prevalent, we speculate that the discussion of proper lens care between physicians and patients has become less routine. Proper cleansing practices should be determined between the patient and his eye care specialist before initiation of CL wear and a review of the process may need to be done periodically.

Those patients who did require surgical intervention seemed to have a poorer visual acuity outcome than those undergoing medical intervention alone (Table 7). It is too soon, however, to interpret these data, because these cases have short follow-up and some are still awaiting secondary procedures such as cataract extraction. These surgical patients need to be

followed up over a longer period for a better assessment of their ultimate postoperative BCVA.

In summary, there has been a significant increase in the incidence of *Fusarium* keratitis at 2 major tertiary eye care centers in the northeastern United States. Our case–control study suggests an association of *Fusarium* keratitis with the use of ReNu contact lens solution. More extensive studies need to be performed to determine the true cause of this outbreak and to improve the clinical outcome of *Fusarium* keratitis. In addition, CL wearers and their physicians should pay particular attention to patients' CL hygiene habits. We encourage that relevant details be discussed between physicians and patients to prevent this sight-threatening condition.

REFERENCES

1. Asbell P, Stenson S. Ulcerative keratitis. Survey of 30 years' laboratory experience. *Arch Ophthalmol*. 1982;100:77–80.
2. Ritterband DC, Seedor JA, Shah MK, et al. Fungal keratitis at the New York eye and ear infirmary. *Cornea*. 2006;25:264–267.
3. Thomas PA. Fungal infections of the cornea. *Eye*. 2003;17:852–862.
4. Liesegang TJ, Forster PK. Spectrum of microbial keratitis in south Florida. *Am J Ophthalmol*. 1980;90:38–47.
5. Alfonso EC, Miller D, Cantu-Dibildox J, et al. Fungal keratitis associated with non-therapeutic soft contact lenses. *Am J Ophthalmol*. 2006;142: 154–155.
6. Rosa RH Jr, Miller D, Alfonso EC. The changing spectrum of fungal keratitis in south Florida. *Ophthalmology*. 1994;101:1005–1013.
7. Tanure MA, Cohen EJ, Sudesh S, et al. Spectrum of fungal keratitis at Wills Eye Hospital, Philadelphia, Pennsylvania. *Cornea*. 2000;19:307–312.
8. Doszi I, Gvetvai T, Kredics L, et al. Involvement of Fusarium spp. in fungal keratitis. *Clin Microbiol Infect*. 2004;10:773–776.
9. Anaissie EJ, Kuchar RT, Rex JH, et al. Fusariosis associated with pathogenic Fusarium species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. *Clin Infect Dis*. 2001;33:1871–1878.
10. Nelson PE, Dignani MC, Anaissie EJ. Taxonomy, biology, and clinical aspects of Fusarium species. *Clin Microbiol Rev*. 1994;7:479–504.
11. Barr J. 2004 Annual Report. *Cont Lens Spectrum*. January, 2005.
12. Liesegang TJ. Contact lens-related microbial keratitis: part I: epidemiology. *Cornea*. 1997;16:125–131.
13. Mah-Sadorra JH, Yavuz SG, Najjar DM, et al. Trends in contact lens-related corneal ulcers. *Cornea*. 2005;24:51–58.
14. Rattanatam T, Heng WJ, Rapuano CJ, et al. Trends in contact lens-related corneal ulcers. *Cornea*. 2001;20:290–294.
15. Schein OD, Ormerod LD, Barraquer E, et al. Microbiology of contact lens-related keratitis. *Cornea*. 1989;8:281–285.
16. Schein OD, Glynn RJ, Poggio EC, et al. The relative risk of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. A case-control study. Microbial Keratitis Study Group. *N Engl J Med*. 1989;321:773–778.
17. Schein OD, Poggio EC. Ulcerative keratitis in contact lens wearers. Incidence and risk factors. *Cornea*. 1990;9:S55–S58.
18. Centers for Disease Control and Prevention (CDC). Fusarium keratitis–multiple states, 2006. *MMWR Morb Mortal Wkly Rep*. 2006;55:400–401.
19. Chang DC, Grant GB, O'Donnell K, et al for the Fusarium Keratitis Investigation Team. Multistate outbreak of Fusarium keratitis associated with use of a contact lens solution. *JAMA*. 2006;296:953–963.
20. Alfonso EC, Cantu-Dibildox J, Munir WM, et al. Insurgence of Fusarium keratitis associated with contact lens wear. *Arch Ophthalmol*. 2006;124: 941–947.
21. Bernal MD, Acharya NR, Lietman TM, et al. Outbreak of Fusarium keratitis in soft contact lens wearers in San Francisco. *Arch Ophthalmol*. 2006;124:1051–1053.
22. Singapore Ministry of Health. Increasing incidence of contact lens related fungal corneal infections (update 3). Available at: http://www.moh.gov.sg/corp/about/newsroom/pressreleases/details.do?id=36077601. Accessed February 21, 2006.
23. Khor W-B, Aung T, Saw S-M, et al. An outbreak of Fusarium keratitis associated with soft contact lens wear in Singapore. *JAMA*. 2006;295: 2867–2873.
24. Tsang T. Fungal keratitis among contact lens users. *Communicable Diseases Watch* [serial on the Internet]. February 5, 2006. http://www.info.gov.hk/dh/diseases/CDwatch/CDW_V3_4.pdf. Accessed April 2006.
25. Research Randomizer. Available at: http://www.randomizer.org/index.htm
26. Optistock MarketWatch – Contact Lens Report – November 2006. Contact lens market: specialty lenses and favorable demographics are driving growth worldwide. Available at: http://www.optistock.com/mw/2002_11all.htm. Accessed April 2006.
27. Marangon FB, Miller D, Giaconi JA, et al. In vitro investigation of voriconazole susceptibility for keratitis and endophthalmitis fungal pathogens. *Am J Ophthalmol*. 2004;137:820–825.
28. Giaconi JA, Marangon FB, Miller D, et al. Voriconazole and fungal keratitis: a report of two treatment failures. *J Ocul Pharmacol Ther*. 2006; 22:437–439.
29. Reis A, Sundmacher R, Tintelnot K, et al. Successful treatment of ocular invasive mould infection (fusariosis) with the new antifungal agent voriconazole. *Br J Ophthalmol*. 2000;84:932–933.
30. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis*. 2003; 36:1122–1131.
31. Wolff M, Bouadma L, Mourvillier B. Emerging azole antifungals. *Therapie*. 2006;61:227–233.
32. Carmen HP, Francisca LT, Amparo BS, et al. Voriconazole in fungal keratitis caused by *Scedosporium apiospermum*. *Ann Pharmacol*. 2004; 38:414–417.
33. Schreiber W, Olbrisch A, Vorwerk CK, et al. Combined topical fluconazole and corticosteroid treatment for experimental *Candida albicans* keratomycosis. *Invest Ophthalmol Vis Sci*. 2003;44:2634–2643.
34. Kaufman HE. Use of corticosteroids in corneal disease and external diseases of the eye. *Int Ophthalmol Clin*. 1966;6:827–843.
35. Stern SA, Buttross M. Use of corticosteroids in combination with antimicrobial drugs in the treatment of infectious corneal disease. *Ophthalmology*. 1991;98:847–853.
36. O'Day DM, Ray WA, Head WS, et al. Influence of corticosteroid on experimentally induced keratomycosis. *Arch Ophthalmol*. 1991;109: 1601–1604.
37. Peponis V, Herz JB, Kaufman HE. The role of corticosteroids in fungal keratitis: a different view. *Br J Ophthalmol*. 2004;88:1227.
38. Jaeger EM, Carroll NM, Choudhury S, et al. Rapid detection and identification of *Candida, Aspergillus*, and *Fusarium* species in ocular samples using nested PCR. *J Clin Microbiol*. 2000;38:2902–2908.
39. Gaudio PA, Gopinathan U, Sangwan V, et al. Polymerase chain reaction based detection of fungi in infected corneas. *Br J Ophthalmol*. 2002;86: 755–760.
40. Kaufman SC, Musch DC, Belin MW, et al. Confocal microscopy: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2004;111: 396–406.
41. Gonçalves AB, Paterson RR, Lima N. Survey and significance of filamentous fungi from tap water. *Int J Hyg Environ Health*. 2006;209: 257–264.
42. Elvers KT, Leeming K, Moore CP, et al. Bacterial-fungal biofilms in flowing water photo processing tanks. *J Appl Microbiol*. 1998;84: 607–618.
43. Kilvington S, Larkin DF, White DG, et al. Laboratory investigation of Acanthamoeba keratitis. *J Clin Microbiol*. 1990;28:2722–2725.
44. Stevenson RW, Seal DV. Has the introduction of multi-purpose solutions contributed to a reduced incidence of Acanthamoeba keratitis in contact lens wearers? A review. *Cont Lens Anterior Eye*. 1998;21: 89–92.