Eye & Contact Lens 32(6): 267–271, 2006

Fungal Keratitis: Emerging Trends and Treatment Outcomes

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Purpose. To review the trends, risk factors, causative organisms, treatment, and outcomes of fungal keratitis at the authors' institution. **Methods.** A retrospective review of the records of consecutive patients diagnosed with fungal keratitis at the authors' institution from January 1999 to June 2006. **Results.** Eighty-four patients were diagnosed with fungal keratitis during this period. The average age of the patients was 48 years, and 64% were male. Until 2004, trauma (51%) and contact lens use (40%) were the major risk factors. After 2005, contact lens use (52%) surpassed trauma as the most common risk factor (29%). The percentage of fungal ulcers caused by nontherapeutic contact lenses increased from 21% between 1999 and 2001 to 32% between 2002 and 2004 and to 45% in 2005 and 2006. Eighty-six percent of cultured organisms were filamentous. *Fusarium* (41%) was the most commonly isolated genus, followed by *Candida* (14%), *Curvularia* (12%), and *Aspergillus* (12%). Visual acuity was worse than 20/200 in 56% of patients at presentation. Final visual acuity was 20/40 or better in 70% of patients treated with medication alone and 16% of patients requiring therapeutic keratoplasty. Surgical intervention in the acute phase was necessary in 23% of patients. Seventy-four percent of medically treated patients had dual topical antifungal therapy. Natamycin 5% and amphotericin B 0.15% were the most commonly used drugs. **Conclusions.** Contact lenses are a major risk factor for fungal keratitis. The incidence of contact lens–related fungal keratitis was increasing even before the *Fusarium* outbreak in 2005 and 2006. Good visual outcomes can be achieved by aggressive dual topical antifungal therapy.
Key Words: Contact lens—Fungal keratitis—*Fusarium*—Ulcers.

Fungal keratitis has received a lot of attention recently because of its association with nontherapeutic contact lenses since 2005.[1–4] Before this period, contact lenses were reported as a predisposing risk factor for fungal keratitis in only 7% to 10% of cases.[5,6] Also, fungal pathogens were rarely isolated in patients with contact lens–related microbial keratitis.[7–11] The recent fungal keratitis epidemic has created much concern because of the perception that this condition has uniformly poor outcomes.[1,12,13] Most ophthalmologists are not familiar with the diagnosis and treatment of fungal keratitis, and this unawareness has led to much panic about the situation. Multiple articles and advisories have been published about the fungal keratitis outbreak.[1,3,14]

At the University of Florida, the authors have seen an increase in the number of fungal keratitis cases in the last several months. However, in contrast to the rest of the country, we routinely see large numbers of fungal keratitis cases. It is primarily the result of the tropical climate because warm, moist environments enhance the growth of fungi.[15] In addition, the authors' institution is a tertiary cornea and external disease referral center that draws from a 100-mile radius with a large agricultural population.[16] Our experience has been that contact lenses are not an uncommon cause of fungal keratitis at our institution even before the *Fusarium* outbreak and that our outcomes of fungal keratitis are much better than those stated in literature. This study was undertaken to determine the major risk factors, causative organisms, and outcomes of fungal keratitis at the authors' institution during a 7.5-year period. In addition, the baseline incidence of contact lens–related fungal keratitis (1999–2004) was evaluated to determine whether there were any trends before the recent outbreak and then was compared to the incidence during the outbreak (2005 and 2006).[17]

MATERIALS AND METHODS

The study was conducted with the approval of the Institutional Review Board of the authors' institution and was designed as a retrospective chart review. Records of all consecutive cases of fungal keratitis diagnosed at the authors' institution from January 1999 to June 2006 were reviewed. Patients were identified by International Classification of Disease, Ninth Revision (ICD-9) diagnosis codes and from the institution's microbiology laboratory database. Inclusion criteria were positive culture for fungus, positive Grocott–Gomori methenamine silver stain (Fig. 1) for fungal elements, or positive histologic result or culture of corneal buttons removed during therapeutic keratoplasty (TKP).

Data collected included patient demographics, date of onset of symptoms, date of presentation to our institution, topical and systemic medications before presentation, predisposing risk factors, visual acuity at presentation, clinical features, laboratory results, frequency and duration of treatment, details of surgical intervention, if any, and visual acuity at final follow-up. All patients were included for the analysis of incidence, risk factors, and laboratory results. However, only patients with at least 1 month of follow-up were included in the treatment and visual outcome analysis. For the purpose of evaluating trends in contact lens–related ulcers, the patients were divided into three groups. Group 1 included patients from January 1999 to December 2001

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Accepted September 29, 2006.

DOI: 10.1097/01.icl.0000249595.27520.2e

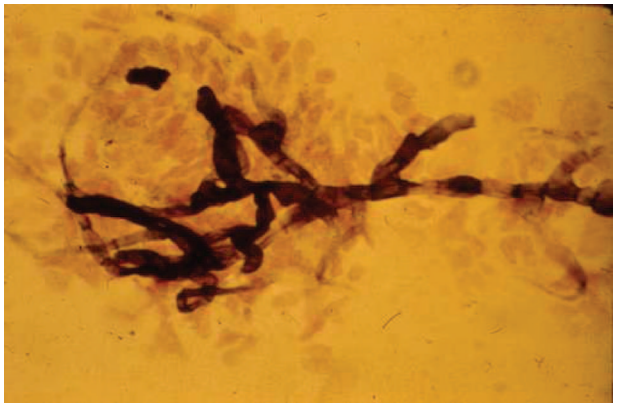

FIG. 1. Grocott–Gomori methenamine silver stain of fungal organisms on corneal scraping (courtesy of William Driebe, Jr., M.D.).

(36 months). Group 2 included patients from January 2002 to December 2004 (36 months), and group 3 included patients from January 2005 to June 2006 (18 months).

RESULTS

Eighty-four cases of fungal keratitis were identified during the study period. The average age of the patients was 48 years (range, 12–94 years). Overall, 64% were male. However, males constituted 75% of patients in groups 1 and 2, but only 35% of patients in group 3. The median time to presentation after the onset of symptoms was 9 days (range, 1–190 days).

Sixty-nine (82%) patients were using topical antimicrobial therapy before presentation. Some had received more than one type of medication. Commercially available antibiotics were the most common (93%), followed by fortified antibiotics (25%), and antivirals (13%). Twelve (17%) patients were already using topical antifungal treatment at the time of presentation. Twenty (29%) patients were using topical steroids at the time of presentation.

Predisposing risk factors were present in 96% (81 of 84) of patients. Some patients had more than one risk factor (Table 1). A history of ocular trauma was present in 36 (43%) patients, and organic matter was involved in 61% of these cases. Trauma remained the most common risk factor (51%) until 2004, followed by contact lenses (40%) and chronic topical steroid use (11%). In the 18 months between January 2005 and June 2006, soft contact lens use (52%) replaced trauma (29%) as the most frequent predisposing risk factor.

TABLE 1. *Risk Factors for Fungal Keratitis*

Risk factors	Group 1 (n = 28)	Group 2 (n = 25)	Group 3 (n = 31)
Trauma	13 (46%)	14 (56%)	9 (29%)
Contact lenses	8 (29%)	13 (52%)	16 (52%)
Nontherapeutic soft contact lenses	6 (21%)	8 (32%)	14 (45%)
Bandage contact lenses	1 (4%)	5 (20%)	2 (6%)
Rigid gas-permeable contact lenses	1 (4%)	0 (0%)	0 (0%)
Chronic topical steroid use	3 (11%)	3 (12%)	3 (10%)
Previous corneal surgery	2 (7%)	3 (12%)	3 (10%)
Ocular surface disorders	3 (11%)	2 (8%)	2 (6%)
Lid abnormalities	2 (7%)	2 (8%)	2 (6%)
Neurotrophic keratopathy	2 (7%)	1 (4%)	2 (6%)
Herpetic eye disease	1 (4%)	1 (4%)	2 (6%)
Diabetes	3 (11%)	2 (8%)	1 (3%)
Systemic steroid use	1 (4%)	1 (4%)	0 (0%)
No risk factors	2 (7%)	0 (0%)	1 (3%)

The total number of cases of fungal keratitis remained relatively stable in group 1 (28 cases in 36 months) and group 2 (25 cases in 36 months) but sharply increased in group 3 (31 cases in 18 months) (Table 2). The number of contact lens–related fungal ulcers increased from eight cases in group 1 to 13 cases in group 2 and 16 cases in group 3. The average yearly incidence was 2.7 in group 1, 4.3 in group 2, and 11 in group 3 (Fig. 2). Nontherapeutic contact lens use alone was a risk factor in 25% (6 of 28) in group 1, 32% (8 of 25) in group 2, and 45% (14 of 31) in group 3.

Eight (10%) patients were using extended-wear bandage contact lenses at the time of the onset of their symptoms. Three patients had the lenses placed for traumatic corneal abrasions and one each for recurrent corneal erosions, bullous keratopathy, exposure keratopathy, corneal laceration, and herpetic stromal disease. One patient was using a daily-wear rigid gas-permeable contact lens after penetrating keratoplasty.

Chronic topical steroid use was recorded in nine patients. Five patients were using corticosteroids as prophylaxis against rejection after penetrating keratoplasty. Two patients had herpetic eye disease; one patient had undergone astigmatic keratotomy and one had undergone a corneoscleral laceration repair recently.

Coexistent ocular disease was present in 16 patients, including five patients with neurotrophic keratopathy, four with herpetic eye disease, three with failed corneal grafts, two with severe dry eye syndrome, one with ocular cicatricial pemphigoid, and one with crystalline keratopathy. Lid abnormalities, including lagophthalmos, traumatic lid coloboma, trichiasis, and cicatricial ectropion, were present in six patients. Diabetes mellitus in six patients and oral steroid use in two patients contributed to systemic immunosuppression.

Patients had stromal infiltrates with feathery borders in 44 (52%) patients (Fig. 3), satellite lesions in 18 (21%), ring infiltrate in 11 (13%), and endothelial plaques in 17 (20%) (Table 3).

Smears of corneal scrapings were stained with Grocott–Gomori methenamine silver stain in 79 (94%) patients and gram stain in 73 (87%) patients. All corneal scrapings were cultured on blood agar, chocolate agar, Sabouraud's agar, and thioglycolate broth. Smear positivity rates were 85% for Grocott–Gomori methenamine silver stain and 25% for gram stain.

Fusarium (41%) was the most commonly isolated fungal organism followed by *Candida* (14%) (Table 3). Two patients had two different fungal species isolated from cultures of their corneal scrapings. Ten (56%) corneal buttons of 18 eyes that required TKP were submitted for culture. Five (50%) of 10 corneal buttons showed fungal growth. Seventeen (94%) corneal buttons were submitted for histopathologic examination, and 13 (76%) of 17 showed fungal elements. Patients with bandage contact lenses showed *Candida* species and *Fusarium* species in equal numbers (43% each). Conversely, nontherapeutic contact lens wearers had *Fusarium* species most frequently (56%), followed by *Aspergillus* species (17%).

Seventy (83%) patients were followed up for 1 month or longer after the diagnosis of fungal keratitis was established and were included in the analysis of outcomes of medical and surgical treatment. Fifty-one (73%) patients needed only medical treatment with topical or systemic antifungal agents, or both. Thirty-six (71%) were treated with two topical antifungal agents (Table 4).

TABLE 2. *Comparison of Total Fungal Keratitis Cases, Contact Lens–Related Fungal Keratitis and Nontherapeutic Contact Lens–Related Fungal Keratitis*

Groups	Total no. of fungal keratitis cases	No. of cases related to contact lens use	Annual incidence of contact lens–related ulcers	Percentage of total fungal ulcers related to contact lens use[a]	Percentage of total fungal ulcers related to nontherapeutic soft contact lens use
1 (1999–2001)	28	8	2.7	29	25
2 (2002–2004)	25	13	4.3	52	32
3 (2005 and 2006)[b]	31	16	11.0	52	45

[a] Includes bandage contact lens use.
[b] Includes 18 months of data.

The most commonly used (61%) combination was natamycin 5% and amphotericin B 0.15%. One patient was treated with three topical antifungals (amphotericin B, fluconazole 1%, and clotrimazole 1%) for concomitant *Candida* and *Acanthamoeba* keratitis. The mean duration of treatment with topical antifungals was 58 days (range, 14–267 days). The average duration of intensive topical therapy (every hour), frequent topical therapy (every 2–4 hours), and regular topical therapy (every 6–24 hours) was 19 days, 24 days, and 19 days, respectively. Systemic antifungal agents were used in addition to topical antifungal therapy in 13 (25%) patients. The mean duration of therapy was 34 days (range, 2–77 days). Oral itraconazole (8 of 13) and oral fluconazole (5 of 18) were the only two systemic antifungal agents used.

Topical steroids were used therapeutically in 16 (31%) patients and were started after an average of 42 days (range, 13–110 days) of topical antifungal treatment. Mean duration of topical steroid therapy was 41 days (range, 8–91 days). One patient had a recurrence of fungal keratitis after initiation of steroids and needed a TKP.

Emergent surgical intervention was needed in 19 patients. TKP was performed in 18 patients, and one patient had an enucleation 5 days after presentation for endophthalmitis with sclerokeratitis. The average duration to TKP after presentation was 17 days (range, 1–102 days). Indications for TKP were corneal perforation (eight patients), impending perforation (four patients), and worsening keratitis with medical treatment (six patients). One of these patients needed an enucleation 2 days after the TKP for recurrence in the corneal graft and endophthalmitis. Corneal gluing was needed in three patients with impending perforation. Only one of these went on to have a TKP. At final follow-up, 12 of the 18 grafts remained clear.

Presenting visual acuity was 20/40 or better in 20 (29%) patients, 20/50 to 20/200 in 17 (24%) patients, and worse than 20/200 in 33 (47%) patients (Fig. 4). After a mean follow-up of 12 months (range, 1–75 months), 39 (56%) patients had visual acuity of 20/40 or better. Of the patients treated with medications alone, 70% had visual acuity of 20/40 or better (Table 5). Only three of the 18 patients who underwent emergent TKP had visual acuity of 20/40 or better.

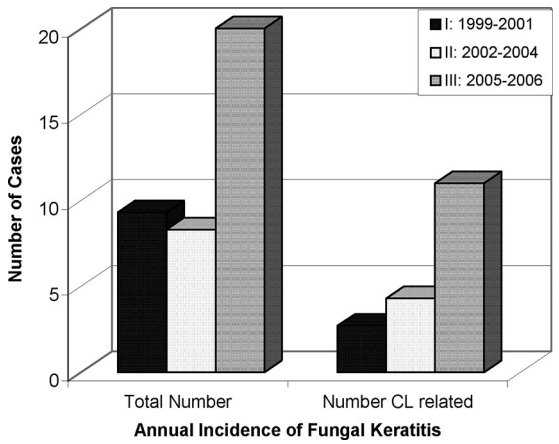

FIG. 2. The annual incidence of all cases of fungal keratitis and contact lens–related fungal keratitis in groups 1 (1999–2001), 2 (2002–2004), and 3 (2005 and 2006).

DISCUSSION

This study reported the trends and outcomes of fungal keratitis at our institution. There has been a lot of attention focused on the recent so-called epidemic of fungal keratitis in soft contact lens wearers in 2005 and 2006 and the possible reasons for it. The conclusion has been that this is an unusual occurrence and has a single inciting factor.[1] However, the main finding of the current study is that the incidence of contact lens–related fungal keratitis has been gradually increasing in the years before 2005, whereas the incidence of the other risk factors has remained stable. Other studies have also seen a similar trend in the incidence of contact lens–related microbial keratitis, although they did not specifically explore fungal ulcers.[8,18]

The reasons for this may be multiple. The number of contact lens wearers has been increasing,[19] and younger individuals are being fitted with contact lenses and may not follow directions for proper care of contact lenses. The mode value of the age of the patients in this study at presentation was 24 years. Also, orthokeratology has resulted in a number of individuals wearing contact

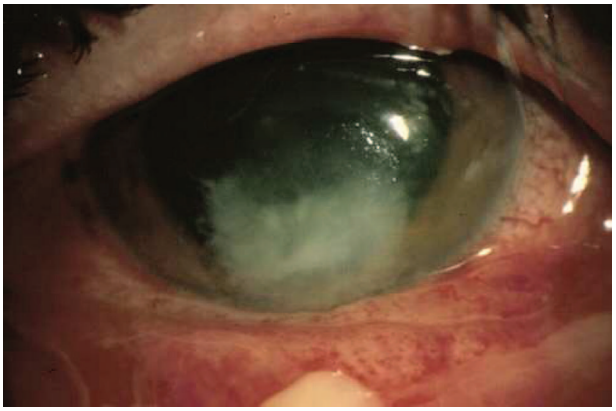

FIG. 3. Fungal corneal ulcer with feathery borders (courtesy of William Driebe, Jr., M.D.).

TABLE 3. *Fungal Isolates in Order of Frequency*

Fungal isolates	No. of isolates (n = 59)	Percentage
Fusarium	24	41
Candida	8	14
Curvularia	7	12
Aspergillus	7	12
Cladosporium	4	7
Penicillium	4	7
Bipolaris	2	3
Phialemonium curvatum	1	1
Trichosporon	1	1
Mycelia sterilia	1	1

lenses overnight.[9,20] Another change has been the shift from peroxide-based solutions toward multipurpose solutions for cleaning and storage of lenses. Multiple studies have shown that these solutions are significantly inferior to peroxide systems for disinfecting contact lenses.[21,22] The recent trend toward no-rub solutions may further compromise the disinfection of lenses.

An interesting demographic feature was the preponderance of males before 2004 and of females after that. This is likely related to the fact that most cases before 2005 were related to trauma, which reflects the findings of other large fungal keratitis studies.[23] The cases after 2005 were predominantly related to contact lenses, and market studies have shown that approximately two thirds of all contact lens wearers are female.[24]

Nearly one third of the patients in this study used topical steroids before the diagnosis of fungal keratitis was established. This is consistent with other studies,[8,25] and topical steroid use could potentially exacerbate the fungal keratitis and lead to worse outcomes.[26,27] Therefore, eye care professionals should be educated about the dangers of using steroids in corneal ulcers before a definitive diagnosis is established.

In this study, 85% of corneal scrapings were positive for fungal elements by Grocott–Gomori methenamine silver stain. Other investigators have also shown that Grocott–Gomori methenamine silver and potassium hydroxide stains have high sensitivity but gram and Giemsa stains have much lower sensitivities.[28–32] Therefore, the authors recommend obtaining smears for Grocott–Gomori methenamine silver stain in every case of contact lens–related keratitis because it can detect fungal elements and *Acanthamoeba*, and results are available much more rapidly than cultures.

Fusarium was the most common organism in this study in all three groups. This is consistent with previous studies from Florida. However, studies performed in the northern United States showed *Candida* to be the most commonly isolated organism.[5,25] This may explain why although the numbers of patients with *Fusarium* keratitis during the recent outbreak in the South were much higher,

TABLE 4. *Topical Antifungal Agents*

Drugs	No.	Percentage
Two antifungal agents	36	71
Natamycin and amphotericin	31	61
Natamycin and voriconazole	4	8
Amphotericin and voriconazole	1	2
One antifungal agent	8	16
Natamycin	4	8
Amphotericin	4	8
Three antifungal agents	1	2
Amphotericin, fluconazole, and clotrimazole	1	2

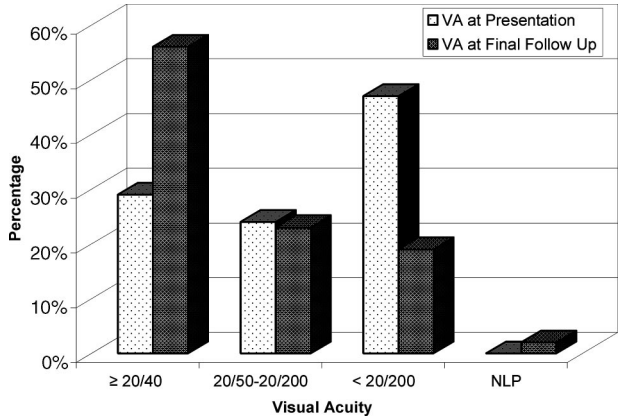

FIG. 4. Visual acuity at presentation and at final follow-up.

it was first recognized in New Jersey with three patients who had developed the keratitis.[4,17]

Most patients in this study were treated with dual antifungal therapy, usually natamycin and amphotericin. Although both are polyene antifungal agents, they have different mechanisms of action as natamycin is more effective against filamentous fungi, whereas amphotericin is more effective against yeast.[33,34] They also differ in their penetration into corneas with intact and absent epithelium.[35–37] Recently, there has also been a trend toward using voriconazole, a triazole antifungal agent, because of its increased safety profile and its different mechanism of action.[38–40] In severe fungal keratitis, it may be beneficial to begin with two different antifungal agents because fungal pathogens differ in their response to antifungal agents and microbiology laboratories do not routinely perform antifungal sensitivities.

The pretreatment visual acuities of patients in this study were poor; nearly half the patients presented with visual acuity less than 20/200. This finding is probably because a large percentage of the patients had advanced disease at presentation. However, visual outcome at the final follow-up was excellent, with more than half having better than 20/40. This is unlike the results at other institutions.[25] One of the reasons for this may be that patients at our institution are treated with antifungal medications soon after presentation based on early recognition of clinical features before laboratory diagnosis. In addition, results of Grocott–Gomori methenamine silver staining are available within 24 hours and have a high sensitivity. Finally, aggressive antifungal therapy with two topical agents is usually instituted until a clinical response is noted. This is different from other reports in which single topical antifungal agents are used and the duration of intensive therapy is much shorter.[31]

This study showed that fungal keratitis was a significant problem in the southern United States, even before the *Fusarium*

TABLE 5. *Visual Acuity at Final Follow-up in Medically and Surgically Treated Groups*

	Medical treatment (n = 51)		Surgical treatment	
Visual acuity at final follow-up	No.	Percentage	No.	Percentage
≥20/40	36	70	3	16
20/50–20/200	10	20	6	32
<20/200	5	10	8	42
No light perception	0	0	2	10

outbreak in 2005 and 2006. Nontherapeutic contact lens use was a significant risk factor even earlier, and the incidence of contact lens–related fungal keratitis was increasing. However, good outcomes can be obtained by aggressive topical antifungal therapy, and most patients have nearly normal vision with medical treatment alone.

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