The Changing Spectrum of Fungal Keratitis in South Florida

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Purpose: To review the clinical experience with fungal keratitis in south Florida over a 10-year period.

Methods: One hundred twenty-five cases of fungal keratitis were identified in the microbiology laboratory records between January 1982 and January 1992. The medical record of each patient was reviewed.

Results: The most commonly associated risk factor was trauma (44%). Fungal keratitis developed in five patients using extended wear contact lenses and one patient wearing a therapeutic bandage contact lens. Clinical features included irregular, feathery margins (62%), a dry, rough texture (47%), and satellite lesions (41%). An initial positive culture was obtained in 90% of patients, with a majority of cultures becoming positive within 48 hours. The Fusarium sp accounted for 62% of the isolates, with Fusarium oxysporum being the most commonly isolated organism. New fungal isolates include Candida parapsilosis, Aspergillus terreus, Candida tropicalis, and Trichosporon beigelli. Natamycin 5% suspension was the initial antifungal agent used for 91% of the patients, with an average duration of treatment of 38 days. Twenty-five patients were treated with oral ketoconazole for a median duration of 2 weeks, in addition to topical antifungal therapy. Thirty-four patients (27%) required a penetrating keratoplasty. Six patients had recurrence of fungal keratitis after penetrating keratoplasty.

Conclusions: Trauma, including contact lens wear, is the most commonly associated risk factor. The fungal organisms can be readily identified in culture. F. oxysporum is the most common organism, with new isolates identified. The mainstay of therapy is topical natamycin with the increasing use of imidazoles.

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Fungal organisms reportedly are isolated from the conjunctival sac in 3% to 28% of healthy eyes. Isolates in healthy eyes have included Aspergillus sp, Rhodotorula sp, Candida sp, Penicillium sp, Cladosporium sp, and Alternaria sp. A higher percentage (17%–37%) of fungi is recovered from diseased eyes. In south Florida, the most common species isolated from the normal outer eye was Candida parapsilosis.

In the last three decades, the number of cases of fungal keratitis has increased dramatically, perhaps attributable to the increased use of topical corticosteroids and broad-spectrum antibiotics. Increased awareness and better diagnostic techniques also have contributed to the increased reporting of fungal keratitis.

The most common organism responsible for fungal keratitis on a worldwide basis is Aspergillus sp. In the northern United States, Candida sp and Aspergillus sp are isolated most frequently in fungal keratitis, whereas Fusarium sp is the major etiologic agent in the southern United States.

In this 10-year retrospective study of 125 patients with fungal keratitis, we report the clinical features, risk factors, diagnosis, medical/surgical treatment, and complications.

Materials and Methods

All cases of fungal keratitis between January 1, 1982, and January 1, 1992, were identified from the records of the
microbiology laboratory at the Bascom Palmer Eye Institute. Specimen collection and recommended culture media have been described previously. A positive fungal culture was defined by (1) a positive smear showing fungal elements and confirmatory growth of a fungus in culture; (2) growth of a fungus on two or more culture media; or (3) growth of a fungus on one medium with growth of the same fungus on at least one medium at a subsequent date.

The Medical Sciences Subcommittee for the Protection of Human Subjects at the University of Miami approved a retrospective review of the medical records of all patients initially identified through the microbiology laboratory records. The data collected from the medical records included the age and sex of each patient, the presenting clinical features, risk factors, medical and/or surgical treatment, and clinical course (including recurrences and complications).

**Results**

**Epidemiology**

One hundred seventeen positive fungal cultures were identified. An additional eight cases of presumed fungal keratitis are included in this review because each had fungal growth on one medium and a clinical presentation/course characteristic of fungal keratitis. Of the patients, 82% were men and 18% were women. The average age at presentation was 49 years. Figure 1 demonstrates the bimodal distribution of occurrence of fungal keratitis in south Florida, with increased frequencies in the Spring and late Fall to early Winter.

**Presenting Clinical Features**

The presenting clinical features of fungal keratitis observed during the slit-lamp examination are listed in Table 1 in decreasing frequency of occurrence.

**Risk Factors**

The risk factors for fungal keratitis are listed in Table 2 in decreasing frequency of occurrence.
Laboratory Diagnosis

An initial Gram and/or Giemsa stain was performed on corneal scrapings in approximately 90% of the patients. Only 71% of the scrapings provided a sufficient specimen (i.e., inflammatory cells, corneal epithelial cells, fungal elements) for interpretation. A positive Gram stain was observed in 33% (27/80). A positive Giemsa stain was observed in 27% (20/74).

Routine culture media included sheep blood agar, chocolate agar, Sabouraud’s agar, and thioglycolate broth. Data regarding the growth of fungi in culture was available in 114 cases. Growth of fungi in culture was first identifiable within 2 days in 54% (62/114), within 3 days in 83% (95/114), and within 1 week in 97% (110/114). A positive initial culture was observed in 90% (113/125) of scrapings. The most common genus isolated was *Fusarium*, accounting for 62% (79/127), with *Fusarium oxysporum* being the most common isolate (37%) using the McGinnis classification scheme for fungal organisms. Table 3 lists all fungal isolates in decreasing frequency of occurrence. Four new fungal isolates not described previously as etiologic agents of fungal keratitis in south Florida include *C. parapsilosis*, *Aspergillus terreus*, *Candida tropicalis*, and *Trichosporon beigelli*. Three patients had documented mixed bacterial-fungal infections (*Pseudomonas* sp in 2 and *Moraxella* sp in 1). One patient had a concomitant herpetic-fungal infection, with a positive herpes simplex virus type 1 immunofluorescent stain. Corneal cultures in two patients showed the simultaneous growth of two different fungi, indicating a mixed fungal keratitis.

A superficial keratectomy or corneal biopsy was performed in 11 patients, in 9 for a diagnosis and in 2 for a recurrence. Cultures of the biopsied specimens in both patients with recurrent fungal keratitis were negative. Cultures of seven of the nine diagnostic corneal biopsies showed fungal growth.

Of 34 patients requiring a therapeutic penetrating keratoplasty, 24 (71%) corneal buttons were submitted to the microbiology laboratory for culture. Sixteen (67%) of 24 corneal buttons showed fungal growth. Results of histopathologic examination of the corneal buttons showed fungal elements in 25 (74%) of 34 patients.

Medical Treatment

A diagnostic and therapeutic corneal scraping/debulking was performed on each patient at presentation. The initial antifungal agent used after the diagnosis of fungal keratitis was 5% natamycin suspension (Pimaricin) in 91% (107/118) of patients. Seven (6%) of 118 patients were started on topical 0.1% to 0.5% amphotericin B. All seven patients had *Candida* sp isolated from the cornea. Four patients with *Candida* sp keratitis were treated successfully with natamycin. Four patients were lost to follow-up before topical antifungal medication was initiated. An additional four patients received no antifungal agents.

Eighty-nine patients (71%) were followed for 3 or more weeks after the diagnosis of fungal keratitis. The average duration of treatment with topical antifungal medication was 38 days. The average duration of intensive topical antifungal therapy (administered at least every 3 hours) was 17 hours and the average duration of nonintensive topical therapy (administered no more than every 4 hours) was 25 days. A second topical antifungal agent was added to 5% natamycin suspension in seven patients, because of the severity of the infection. These included 0.15% to 0.20% amphotericin B (2 patients), 1% miconazole (4 patients), and 1% 5-fluorocytosine (1 patient).

Systemic antifungal agents were used in 27 patients with severe keratitis, scleritis, and endophthalmitis. These agents included oral ketoconazole (200–400 mg every day) (n = 25), intravenous amphotericin B (0.5–1.0 mg/kg daily) and intravenous miconazole (1000 mg every 8 hours) (n = 1), and fluconazole (100 mg every day) (n = 1). Oral ketoconazole was prescribed in combination with topical antifungal medication for a median duration of 2 weeks.

Subconjunctival antifungal agents, including amphotericin B (0.1 mg) and miconazole (5–10 mg), were used in ten patients with severe fungal keratitis requiring penetrating keratoplasty (n = 3), keratoscleritis requiring cor-
neoscleral transplantation (n = 2), and secondary endophthalmitis (n = 5).

Sixteen patients received from one to five intraocular injections of amphotericin B (5 μg/0.1 ml). Eight patients with severe fungal keratitis and the suspicion of endophthalmitis received intraocular injections of amphotericin B at the time of penetrating keratoplasty. In eight patients, endophthalmitis with fungal isolation from vitreous and aqueous specimens was diagnosed on clinical examination.

Nineteen patients received topical corticosteroids to decrease corneal inflammation and scarring after the diagnosis of fungal keratitis and after a period of treatment (average, 14 days) with topical antifungal therapy. The average duration of treatment with topical corticosteroids in 17 of the 19 patients was 24 days. On clinical examination, the conditions of two patients worsened while receiving corticosteroid therapy. These two patients were started on corticosteroids within 1 to 3 days of starting topical antifungal therapy. In six patients, topical corticosteroids were used to decrease inflammation for an average period of 10 days before therapeutic penetrating keratoplasty.

Surgical Treatment

Thirty-four (27%) of 125 patients required a therapeutic penetrating keratoplasty for fungal keratitis. The procedure was performed in 74% (25/34) within 4 weeks after presentation (Fig 2). Reasons for proceeding with a penetrating keratoplasty included overwhelming fungal infection without significant response to medical therapy alone (n = 19), corneal perforation (n = 11), and recurrence of fungal keratitis on medical therapy (n = 4). Of 34 patients, 5 required a second penetrating keratoplasty, 8 for graft failure and 3 for recurrence of fungal keratitis. F. oxysporum was isolated in all three patients with recurrent fungal keratitis requiring a second penetrating keratoplasty. Cryotherapy was used in one patient with recurrent F. oxysporum keratoscleritis after penetrating keratoplasty. The most common fungal isolates in patients requiring a penetrating keratoplasty in order of decreasing frequency of occurrence are listed in Table 4. A partial conjunctival flap was performed at the time of penetrating keratoplasty in one patient, and after a lateral tarsorrhaphy in a second patient.

Other Surgical Procedures

A total of six patients with a history of exposure keratopathy were treated with a lateral tarsorrhaphy. In five of six patients, C. parapsilosis was isolated from corneal cultures. Seven of 125 patients required a lensectomy or intra-/extracapsular cataract extraction ± anterior vitrectomy ± iridectomy in conjunction with the therapeutic penetrating keratoplasty. A pars plana vitrectomy was performed within 2 weeks of the presenting date in five patients with secondary fungal endophthalmitis. Of 125 patients, 4 required an enucleation for overwhelming fungal infections secondary to F. oxysporum (n = 1), Acremonium sp (n = 1), A. terreus (n = 1), and Lasiodiplodia theobromae (n = 1).

Complications

A corneal perforation was observed in 13 patients (10%) with fungal keratitis. Three patients had a corneal perforation at the time of presentation, with the remainder occurring between 4 and 55 days after the presenting date. Five of 13 patients were treated with topical corticosteroids before the development of a corneal perforation. All 13 patients required a therapeutic penetrating keratoplasty. Fungal organisms isolated in patients with a corneal perforation included F. oxysporum (n = 4), F. solani (n =

Table 4. Fungal Isolates in Patients Requiring Therapeutic Penetrating Keratoplasty in Order of Decreasing Frequency of Occurrence

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusarium</td>
<td>22</td>
</tr>
<tr>
<td>F. oxysporum</td>
<td>13</td>
</tr>
<tr>
<td>F. solani</td>
<td>7</td>
</tr>
<tr>
<td>F. moniliforme</td>
<td>1</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1</td>
</tr>
<tr>
<td>Candida</td>
<td>4</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>3</td>
</tr>
<tr>
<td>C. albicans</td>
<td>1</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>3</td>
</tr>
<tr>
<td>A. terreus</td>
<td>1</td>
</tr>
<tr>
<td>A. flavus</td>
<td>1</td>
</tr>
<tr>
<td>A. fumigatus</td>
<td>1</td>
</tr>
<tr>
<td>Acremonium</td>
<td>2</td>
</tr>
<tr>
<td>Curvularia</td>
<td>2</td>
</tr>
<tr>
<td>C. senegalensis</td>
<td>2</td>
</tr>
<tr>
<td>Cylindrocarpon</td>
<td>1</td>
</tr>
</tbody>
</table>

* Mixed fungal infection with Trichosporon beigelii.
3), F. moniliforme (n = 1), A. fumigatus (n = 1), A. flavus (n = 1), C. albicans (n = 1), C. parapsilosis (n = 1), and Acremonium sp (n = 1). Two patients received a diagnosis of keratoclastic keratitis secondary to F. oxysporum. Endophthalmitis was diagnosed in ten patients with fungal keratitis. Four patients had endophthalmitis, and endophthalmitis developed in an additional four patients within 2 weeks of presentation. Endophthalmitis developed in the remaining two patients 19 and 42 days after presentation.

Fungal isolates cultured in patients with endophthalmitis included F. oxysporum (n = 4), F. solani (n = 1), Acremonium sp (n = 2), A. terreus (n = 1), Cylindrocarpon sp (n = 1), and L. theobromae (n = 1). In six patients, a recurrence of fungal keratitis developed after penetrating keratoplasty within 1 to 2 weeks, except in one patient in whom the recurrence developed nearly 2½ months after penetrating keratoplasty. Fungal isolates in these six patients with recurrence after penetrating keratoplasty included F. oxysporum (n = 4), F. solani (n = 1), and Acremonium sp (n = 1).

Discussion

One hundred twenty-five cases of fungal keratitis were diagnosed between January 1982 and January 1992 at the Bascom Palmer Eye Institute in Miami, Florida. Fungal keratitis remains a major cause of visual loss among infectious diseases of the cornea in south Florida. In this and previous series from south Florida, trauma is cited as the major risk factor for fungal keratitis, accounting for 44% of cases in the current study.11,12,14 Trauma, specifically in the outdoor environment, was reported in 26% of patients, with 17% reporting trauma with vegetable matter. Trauma is associated with fungal keratitis in the world literature in 33% to 100% of patients in various series.10,13-23 Clinch and associates24 reported three patients with fungal keratitis from nylon-line lawn trimmers, with two cases secondary to Curvularia sp. In two patients in the current series, fungal keratitis associated with trauma developed while using a nylon-line lawn trimmer. The fungal isolates in these patients included F. oxysporum and C. parapsilosis.

Extended-wear contact lenses and therapeutic bandage contact lenses appear to be a risk factor for fungal keratitis. Six patients in the current series wore extended-wear contact lenses, two of whom were aphakic. Fungal isolates in these patients included F. oxysporum (n = 4), C. albicans (n = 1), and Paecilomyces sp (n = 1). In one patient with pseudophakic bullous keratopathy who wore a bandage contact lens, a C. parapsilosis keratitis developed. Liebsegang and Forster11 reported three patients with fungal keratitis wearing soft contact lenses, two of which were worn for therapeutic purposes. Fungal isolates in these three patients included C. albicans, A. flavus, and Fusarium dimerum. In two series of ulcerative keratitis associated with contact lens wear in south Florida, Alfonso and colleagues25,26 found fungal organisms (Fusarium sp and others) in 2 patients of 64 patients who had culture-positive results in one series and none in the second series.

Smolin and associates27 studied the microbial flora in extended-wear soft contact lens wearers and recovered C. albicans (n = 1) and Rhodotorula sp (n = 1) in a total of 44 of 857 positive cultures of material collected from 51 soft contact lens wearers. Fungal growth within the matrix of aphakic soft contact lenses has been reported.28,29 Other reports in the literature include fungal keratitis associated with a "piggyback-type" contact lens after penetrating keratoplasty (C. parapsilosis).57 Fusarium in gram of a therapeutic bandage contact lens worn for a metaherpetic corneal epithelial erosion with a secondary Cephalosporium acremonium keratitis; F. solani keratitis associated with daily wear soft contact lenses.30-32 Wilhelmus and colleagues33,34 reported fungal infection in 4 (4%) of 90 cosmetic or aphakic contact lens wearers and in 4 (27%) of 15 using a therapeutic bandage contact lens, with filamentous fungi more likely associated with cosmetic or aphakic lens wear and yeasts more frequently found with therapeutic lens use.

Twelve percent of the patients had diabetes, whereas the prevalence of diabetes mellitus in the general population is 1%.35

In the laboratory diagnosis of fungal keratitis, the most common initial stains used are the Gram and Giemsa stains. In the current series, a positive Gram stain was observed in 33% (27/80) of patients and a positive Giemsa stain in 27% (20/74). The percentages of positive stains showing fungal elements are less than in previous studies in south Florida, where 80% of Gram stains and 54% to 66% of Giemsa stains were positive.11,12,36 Jones37 reported the detection of hyphal fragments of filamentous fungi or blastospores or pseudohyphae of yeasts in 32 (78%) of 41 cases of fungal keratitis. Routine culture media in the current series included sheep blood agar, chocolate agar, Sabouraud's agar, and thioglycolate broth, with growth of fungi first identifiable within 3 days (72 hours) in 83.3%. Jones38 found that 77% of filamentous fungi and yeasts grew in one or more media within 3 days of inoculation.

Fusarium was the most common genus isolated, accounting for 62% (79/127) of all fungal isolates. Fusarium sp was isolated in 39 (71%) of 55 patients with trauma as a risk factor for fungal keratitis (Table 5). F. oxysporum was the most common species (37%), followed by F. solani (24%), using the McGinnis classification scheme for fungal organisms.13 Candida sp, Curvularia sp, and Aspergillus sp were the next most common fungal isolates in order of decreasing frequency. In two previous series from south Florida between 1959 and 1977, Fusarium sp accounted for 76% of fungal keratitis in an early study and 61% in a later study, with F. solani specifically isolated in 29% and 57% of cases, respectively.11,14 F. oxysporum was isolated once in each of the two previous series. Fusarium sp have been isolated from the cornea in cases of fungal keratitis throughout the world, including North, Central, and South America, Europe, Africa, the Middle East, India, China, and Japan.15,19,20,38-40 F. solani was considered the most important cause of keratomycosis.41 The largest series of fungal keratitis outside of south Florida are reported from India. The most common fungal isolate
in India is *Aspergillus* sp (27%-64%), followed by *Penicillium* sp (2%-29%), and *Fusarium* sp (6%-32%).16-18,20-22 Poria and colleagues16 reported *Fusarium* sp (12 of 37 patients, or 32%) as the most common fungal isolate in a coastal region of east central India. In the northern United States, *Candida* sp and *Aspergillus* sp are the most frequent isolates in fungal keratitis.5-10,42 In the current series, *Candida* sp was isolated more frequently in patients with chronic ocular disease and in association with the use of chronic topical medications, including topical corticosteroids (Table 5).

Four new fungal organisms not previously described as etiologic agents of fungal keratitis in south Florida were isolated and include *Candida parapsilosis*, *Candida tropicalis*, *Aspergillus terreus*, and *Trichosporon beigeli*. Of 12 patients, (75%) 9 with the new *Candida* sp isolates had a history of a locally compromised ocular status such as exposure keratopathy, herpetic neurotrophic disease, and pseudophakic bullous keratopathy.

Seven of 11 corneal biopsies showed the growth of fungi in culture. The corneal biopsy was performed in nine patients for diagnostic purposes and in two patients to detect fungal growth after worsening while receiving medical treatment. Ishibashi and Kaufman45 evaluated the usefulness of corneal biopsy in the diagnosis of keratomycosis in experimental fungal keratitis in rabbits. Of ten specimens, corneal scrapings disclosed three that were positive for *C. albicans*, five for *F. solani*, and six for *A. fumigatus* keratitis, whereas corneal biopsy specimens showed fungal elements in all inoculated eyes. Ishibashi and Kaufman later compared the value of direct examination and culture of biopsy specimens in the diagnosis of keratomycosis in rabbits with experimental fungal keratitis caused by *F. solani*, *A. fumigatus*, and *C. albicans*. Of ten specimens, cultures disclosed seven that were positive for *C. albicans* and eight that were positive for *F. solani* and *A. fumigatus* keratitis, whereas direct examination showed positive fungal elements in all specimens.44 The above studies suggest that corneal biopsy is superior to corneal scraping and that direct examination of corneal biopsy specimens is superior to cultures in the diagnosis of fungal keratitis.

The initial antifungal agent was 5% natamycin, which was used in 91% (107/118) of patients in this series, with an average duration of treatment of 38 days. In the earliest series of fungal keratitis from south Florida, Jones and colleagues44 reported an average duration of treatment with natamycin of 27 days. Jones and associates45 later reported 18 consecutive patients with *F. solani* keratitis treated with natamycin for an average of 30 days. The initial reports of success with topical natamycin therapy in fungal keratitis involved the filamentous fungi, in particular, the *Fusarium* sp.14,45,46 Amphotericin B was the initial antifungal agent in seven patients with *Candida* sp keratitis in the current series. Four patients with *Candida* sp keratitis were treated successfully with natamycin. Review of the literature indicates that the initial drug of choice in fungal keratitis is 5% natamycin suspension; with the possible exception of *Candida* sp keratitis, in which amphotericin B may be the drug of choice.37,47,48 A 0.15% concentration of topical amphotericin B is typically sufficient to treat fungal keratitis and avoid ocular toxicity from higher concentrations.49

Newer antifungal agents have been used on a sporadic basis since the introduction of natamycin. The azole group of antifungal agents, including the imidazoles and the newer triazoles, have been examined both experimentally and clinically in the treatment of fungal keratitis. Synergy studies have been conducted to examine the effect of treatment with combinations of antifungal agents. Searl and colleagues50 found a synergistic effect in vitro when 5-flucytosine was combined with either miconazole or natamycin in the treatment of *Aspergillus* sp keratitis. Oral ketoconazole (200-400 mg daily) was prescribed in 25 patients and fluconazole (100 mg daily) in one patient with fungal keratitis in the current series. The median duration of therapy with ketoconazole was 2 weeks. Of 25 patients, 9 (36%) taking a combination of oral ketoconazole and topical antifungal therapy did not require

Table 5. Major Organisms Isolated in the Four Most Common Risk Factor Groups in Order of Decreasing Frequency of Occurrence

<table>
<thead>
<tr>
<th>Trauma (n = 56)*</th>
<th>Chronic Topical Medications (n = 16)</th>
<th>Diabetes Mellitus (n = 15)†</th>
<th>Topical Corticosteroids (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism No. (%)</td>
<td>Organism No. (%)</td>
<td>Organism No. (%)</td>
<td>Organism No. (%)</td>
</tr>
<tr>
<td><em>Fusarium</em> 39 (70)</td>
<td><em>Candida</em> 7 (44)</td>
<td><em>Fusarium</em> 10 (67)</td>
<td><em>Candida</em> 2 (22)</td>
</tr>
<tr>
<td><em>Curvularia</em> 6 (11)</td>
<td><em>Fusarium</em> 6 (38)</td>
<td><em>Candida</em> 2 (13)</td>
<td><em>Aspergillus</em> 2 (22)</td>
</tr>
<tr>
<td><em>Aspergillus</em> 3 (5)</td>
<td><em>Other</em> 3 (18)</td>
<td><em>Other</em> 3 (20)</td>
<td><em>Acremonium</em> 2 (22)</td>
</tr>
<tr>
<td><em>Other</em> 8 (14)</td>
<td></td>
<td></td>
<td><em>Curvularia</em> 2 (22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Fusarium</em> 1 (12)</td>
</tr>
</tbody>
</table>

* Two organisms were isolated in one patient with a mixed fungal infection; hence, 56 organisms were isolated in 55 patients with trauma as a risk factor.
† Nine patients with diabetes mellitus had a history of trauma. Three patients were taking chronic topical medications (including one patient who was taking chronic topical corticosteroids). Of the remaining three patients, one had undergone post-penetrating keratoplasty and the other two patients denied any history of trauma or other significant risk factors.
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a therapeutic penetrating keratoplasty or other major surgical intervention in the management of fungal keratitis. Systemic agents were used in 21 patients with severe or worsening keratitis, in 5 patients with endophthalmitis, and in 1 patient with keratocleritis. In our experience, the increased use of imidazoles has not paralleled a decrease in the severity or complications of fungal keratitis.

Several clinical and experimental studies have reported favorable results in the treatment of fungal keratitis with both topical and systemic ketoconazole. In contrast, Komadina and associates studied a rabbit model of *A. fumigatus* keratitis and found that neither topical nor oral ketoconazole was effective, despite moderate in vitro sensitivity. However, when used in conjunction with nataomycin, oral and topical ketoconazole appeared to augment the sterilization of *A. fumigatus* in the rabbit model. Fitzsimons and Peters reported the successful treatment of fungal keratitis (including *Fusarium* sp, *Aspergillus* sp, *Drechslera* sp, and *Candida* sp) with topical and subconjunctival miconazole in combination with oral ketoconazole in 13 of 20 patients. Mohan and co-workers conducted an unmasked prospective study to evaluate the efficacy of topical 1% miconazole in the treatment of human keratomycosis. Of 85 patients, 45 (65%) were considered successfully treated, with an average healing time of 22 days. The efficacy of 1% miconazole was greatest in *Candida* sp (4 of 5, or 80% positive response), followed by *Aspergillus* sp (14 of 20, or 70%), and *Fusarium* sp (3 of 6, or 50%).

Fifteen percent (n = 19) of the patients in this study received topical corticosteroids to decrease corneal inflammation and scarring after the diagnosis of fungal keratitis and after a period of antifungal therapy averaging 14 days. The average duration of treatment with topical corticosteroids was 24 days. Two of 19 patients were started on topical corticosteroids within 1 to 3 days of beginning topical antifungal therapy, and their conditions worsened on clinical examination. An association between topical corticosteroid administration and the development and/or worsening of fungal keratitis has been recognized for some time. Corticosteroids may activate non-pathogenic fungi and increase the virulence of pathogenic fungi. Forster and Rebell studied an animal model of *F. solani* keratitis and found that to produce progressive culture-positive ulcers in a high percentage of rabbit eyes 2 and 3 weeks after inoculation, administration of subconjunctival corticosteroids was necessary before treatment. O'Day and colleagues reported that the efficacy of 0.5% and 0.15% amphotericin B and 1% amphotericin B methyl ester appeared unaffected when used in conjunction with topical 1% prednisolone acetate in a rabbit model of *Candida* keratitis; however, the rabbit's condition worsened when given corticosteroid alone, or the drug adversely influenced the efficacy of 5% natamycin, 1% miconazole, and 1% flucytosine when given in combination. Stern and Buttrose concluded that topical corticosteroids are contraindicated in the treatment of fungal keratitis.

In 34 (27%) of 125 patients, a therapeutic penetrating keratoplasty was performed typically within 4 weeks of presentation (74%) for medical treatment failure (56%), corneal perforation (32%), and recurrent keratitis while receiving medical therapy (12%). A repeat penetrating keratoplasty was required in eight patients, five for graft failure and three for recurrent *F. oxysporum* keratitis. A higher percentage of fungal infections seems to result in medical treatment failures or corneal perforations than other causes of microbial keratitis. In an earlier study in south Florida, 18% of patients were treated with a penetrating keratoplasty. Forster and Rebell reported 15% of patients with fungal keratitis in a later study who required penetrating keratoplasty. Perhaps the increase in the number of patients requiring keratoplasty in the current study is related to a delay in the diagnosis of fungal keratitis, because of the increasing use of empiric therapy with topical antibiotics and/or corticosteroids in the treatment of microbial keratitis. A repeat penetrating keratoplasty was performed typically within 4 weeks of presentation (74%) for medical treatment failure (56%), corneal perforation (32%), and recurrent keratitis while receiving medical therapy (12%). A repeat penetrating keratoplasty was required in eight patients, five for graft failure and three for recurrent *F. oxysporum* keratitis. A higher percentage of fungal infections seems to result in medical treatment failures or corneal perforations than other causes of microbial keratitis. In an earlier study in south Florida, 18% of patients were treated with a penetrating keratoplasty. Forster and Rebell reported 15% of patients with fungal keratitis in a later study who required penetrating keratoplasty. Perhaps the increase in the number of patients requiring keratoplasty in the current study is related to a delay in the diagnosis of fungal keratitis, because of the increasing use of empiric therapy with topical antibiotics and/or corticosteroids in the treatment of microbial keratitis. A therapeutic penetrating keratoplasty may be indicated in cases of medical treatment failure and corneal perforation and for visual rehabilitation.

### References