CURVULARIA KERATITIS*

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ABSTRACT

Purpose: To determine the risk factors and clinical signs of *Curvularia* keratitis and to evaluate the management and outcome of this corneal phæohyphomycosis.

Methods: We reviewed clinical and laboratory records from 1970 to 1999 to identify patients treated at our institution for culture-proven *Curvularia* keratitis. Descriptive statistics and regression models were used to identify variables associated with the length of antifungal therapy and with visual outcome. In vitro susceptibilities were compared to the clinical results obtained with topical natamycin.

Results: During the 30-year period, our laboratory isolated and identified *Curvularia* from 43 patients with keratitis, of whom 32 individuals were treated and followed up at our institute and whose data were analyzed. Trauma, usually with plants or dirt, was the risk factor in one half; and 69% occurred during the hot, humid summer months along the US Gulf Coast. Presenting signs varied from superficial, feathery infiltrates of the central cornea to suppurative ulceration of the peripheral cornea. A hypopyon was unusual, occurring in only 4 (12%) of the eyes but indicated a significantly (P = .01) increased risk of subsequent complications. The sensitivity of stained smears of corneal scrapings was 78%. *Curvularia* could be detected by a panfungal polymerase chain reaction. Fungi were detected on blood or chocolate agar at or before the time that growth occurred on Sabouraud agar or in brain-heart infusion in 83% of cases, although colonies appeared only on the fungal media from the remaining 4 sets of specimens. *Curvularia* was the third most prevalent filamentous fungus among our corneal isolates and the most common dematiaceous mold. Corneal isolates included *C senegalensis*, *C lunata*, *C pallescens*, and *C prasadii*. All tested isolates were inhibited by 4 μg/mL or less of natamycin. Topical natamycin was used for a median duration of 1 month, but a delay in diagnosis beyond 1 week doubled the average length of topical antifungal treatment (P =.005). Visual acuity improved to 20/40 or better in 25 (78%) of the eyes.

Conclusions: *Curvularia* keratitis typically presented as superficial feathery infiltration, rarely with visible pigmentation, that gradually became focally suppurative. Smears of corneal scrapings often disclosed hyphae, and culture media showed dematiaceous fungal growth within 1 week. Natamycin had excellent in vitro activity and led to clinical resolution with good vision in most patients with corneal curvulariosis. Complications requiring surgery were not common but included exophytic inflammatory fungal sequestration, treated by superficial lamellar keratectomy, and corneal perforation, managed by penetrating keratoplasty.

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INTRODUCTION

Fungal infections of the eye are a growing threat that have substantial morbidity and cost.[1] *Aspergillus* and *Fusarium* are long recognized as ocular pathogens,[2] but the dematiaceous hyphomycetes have emerged as important opportunists.[3-6] Originally named for their tufted, floccose appearance in culture, dematiaceous fungi comprise those septate molds with melanin in their hyphae and conidia.[7]

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Curvularia is a prevalent member of these darkly pigmented fungi that received its current name in 1933[8] and that is related to the sexual teleomorph *Cochliobolus*.

This genus of filamentous fungi colonizes soil and vegetation and spreads by airborne spores. Some of the 40 *Curvularia* species are phytopathogens. Plant diseases range from seedling failure to leaf blight,[9] including grass "fade out" during hot, humid weather. Curvularial growth on stored grain, thatch, and other dead plant material looks like smudges of blackish dust.

Several *Curvularia* species are zoopathogenic. Wound infection is the most common disease caused by *Curvularia* and ranges from onychomycosis to skin ulceration and subcutaneous mycetoma.[10,11] Other human *Curvularia* infections are invasive and allergic sinusitis and bronchopulmonary disease. Abscesses of the lung,

brain, liver, and connective tissue have occurred. Nosocomial infections include dialysis-related peritonitis and postsurgical endocarditis.[12]

Infection of the cornea, reported in 1959,[13] was the first human disease proved to be caused by *Curvularia*. Other ocular infections consist of conjunctivitis,[14] dacryocystitis,[15,16] sino-orbital cellulitis,[17] and endophthalmitis.[14,18-20] But the cornea is the most commonly infected site.[2,3,13,14,21-88] To describe the clinical spectrum and management of *Curvularia* keratitis, we reviewed our experience with this corneal phæohyphomycosis.

METHODS

Cases of culture-positive *Curvularia* keratitis were identified by reviewing the records of our ocular microbiology laboratory for patients with keratomycosis. Patients evaluated for this study were treated and followed at the Cullen Eye Institute in Houston, Texas, between 1970 and 1999. At the initial examination, demographic and other data were recorded onto medical record forms. The diameter (d) of the stromal infiltrate was generally measured with a slit-beam reticule or eyepiece micrometer. The infiltrate area was then estimated by $\pi d^2/4$, rounding to the nearest 0.5 mm^2. Additional information on risk factors, clinical features, laboratory data, interventions, and outcomes were collected from outpatient, hospital, photographic, microbiologic, and pathologic files and entered onto computerized spreadsheets.

Climatic information was downloaded from the online weather database provided by the National Climatic Data Center of the National Oceanic and Atmospheric Administration, US Department of Commerce. We averaged monthly data on temperatures recorded by 100 stations along the upper coast of Texas from 1970 through 1999.

Corneal scrapings were routinely smeared onto glass slides for gram, Giemsa, acridine orange, and/or calcofluor white staining and were inoculated directly onto culture media that typically included a blood agar plate, a chocolate agar plate, a thiol or thioglycolate liquid, an anaerobic medium such as *Brucella* or Schaedler agar (each incubated at 35°C), Sabouraud dextrose agar plate or slant, and brain-heart infusion (BHI) broth (both incubated at 25°C).[89] The minimal requirements for laboratory confirmation of *Curvularia* corneal infection were either a stained smear showing filamentous fungal elements with growth of *Curvularia* on at least 1 medium or isolation of *Curvularia* on at least 2 different primary media.

Dematiaceous fungal growth was recognized as pigmented colonies on C-streaks of primary culture media. *Curvularia* produced woolly olive-brown or black colonies, occasionally with a slate-blue sheen (Fig 1A and 1B). Rapidly growing mycelia often produced a central depression in the dark, matted colony. Slide culture showed the characteristic microscopic appearance of branched, septate, tawny hyphae and short, nodose, brown conidiophores bearing single and clustered septate conidia (Fig 1C). Speciation was based on the microscopic appearance of conidia.[90,91] The minimum inhibitory concentration (MIC) was determined for selected isolates with antibiotic-saturated paper discs in multiwell plates[92]

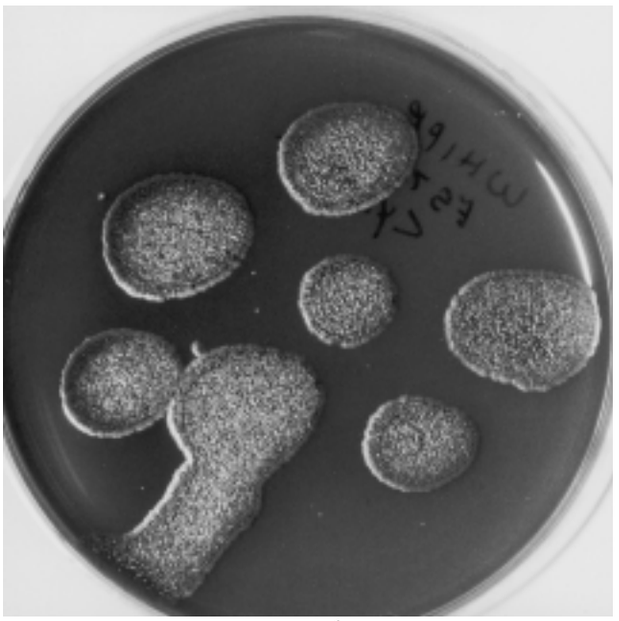


FIGURE 1A
Case 15. Dematiaceous fungal growth on blood agar from corneal scrapings.

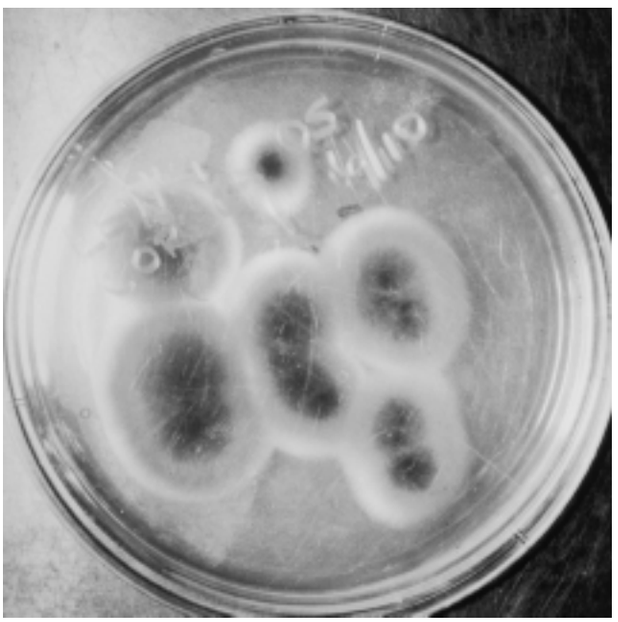


FIGURE 1B
Case 15. Pigmented colonies on Sabouraud agar at several inoculation sites.

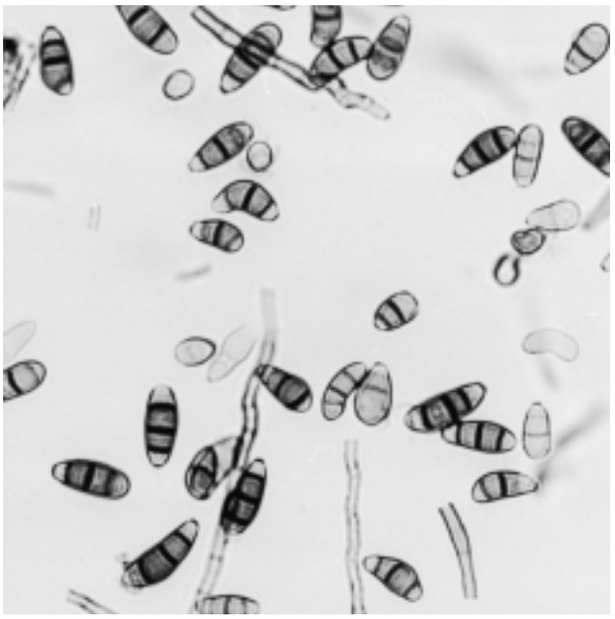


FIGURE 1C
Case 23. Septate hyphae and curved conidia on slide culture.

or by a broth-dilution technique.[93] The minimum fungicidal concentration (MFC) was determined by subcultures from the MIC microwells onto blood agar plates.

Logistic regression assessed correlations between exposure variables and both the visual outcome and the duration of antifungal treatment. Visual outcome was dichotomized based on final visual acuity better than 20/50 without surgical intervention. The breakpoint for dividing the duration of topical antifungal treatment into 2 groups was 30 days. Independent variables considered for inclusion in regression models were patient age, predisposing factor, prior corticosteroid or antibiotic use before diagnosis, duration until diagnostic evaluation, size of corneal infiltrate, and hypopyon status. Linear regression was used to explore the association of exposure variables on the duration of antifungal therapy. Regression models were performed using Stata 6.0 (College Station, Texas).

For molecular analysis, nucleic acid was extracted from culture specimen pellets with phenol:chloroform:isoamyl alcohol, precipitated with ethanol, and resuspended in tris-EDTA buffer. Fungal DNA was amplified using the polymerase chain reaction (PCR). The primer was based on the highly conserved 5.8s ribosomal RNA, internal transcribed sequence-2, and 25s rRNA regions.[94] Thermocycling was performed at 94ºC, 58ºC, and 72ºC for 30 cycles. The PCR product was resolved on an agarose tris-borate-EDTA gel, visualized with ethidium bromide under ultraviolet light, and compared to positive and negative controls.

A murine model of *Curvularia* keratitis was attempted by scarifying the right cornea and applying a concentrated fungal inoculum using a protocol approved by our institutional animal care and use committee. Ten NIH Swiss female mice (Harlan Sprague Dawley, Indianapolis, Indiana) were used, of which 4 were pretreated with intramuscular methylprednisolone (Depo-Medrol, Pharmacia & Upjohn, Kalamazoo, Michigan) 100 mg/kg 4 days before inoculation. Following anesthesia with ketamine:xylazine:acepromazine, the cornea was scratched with a 25-gauge needle in a 6 x 6 linear grid pattern. A dark sludge of freshly grown *C lunata*, originally isolated from a human corneal infection (case 30), was prepared in phosphate-buffered saline to yield the spectrophotometric equivalent of either 10^6 or 10^8 cells per 5 mL. One of these inocula was applied to the corneal surface, and the eyelids were rubbed together. Eyes were observed daily to detect corneal inflammation and were examined histopathologically after euthanasia.

RESULTS

CLINICAL SUMMARY

Of 43 patients with *Curvularia* keratitis diagnosed by our laboratory, 32 were treated at our institute (Table I). All but 1 case began near the upper Texas or Louisiana coast (Fig 2). Average patient age was 43 ± 21 years, including 5 (16%) less than 12 years old. Thirty patients (94%) were males, and 20 cases (62.5%) occurred in left eyes. Sixteen (50%) involved injury with plant or dirt material. Twenty-two (69%) of the cases began during the hot, humid months of June, July, August, and September (Fig 3). Only 5 patients (16%) were correctly diagnosed as having fungal infection on their first examination. Twenty (62.5%) were initially thought to have bacterial keratitis; 2 were treated for herpes simplex virus keratitis; and 5 were first considered to have sterile or toxic inflammation. A

FIGURE 2
Regional map showing sites along US coast of the Gulf of Mexico where patients developed *Curvularia* keratitis.

TABLE 1: CLINICAL CHARACTERISTICS OF CASES *CURVULARIA* KERATITIS

CASE	YEAR	AGE	SEX	RACE	EYE	TRAUMA	INITIAL KERATITIS DIAGNOSIS	CORTICOSTEROID BEFORE DIAGNOSIS	ANTIBACTERIAL BEFORE DIAGNOSIS	DAYS UNTIL ANTIFUNGAL THERAPY	AREA (MM^2) OF CORNEAL INFILTRATE	HYPOPYON
1	1972	29	M	B	L	ND	Fungal	N	N	3	5	N
2	1973	68	M	W	L	Sawdust	Fungal	N	N	1	8	N
3	1973	48	M	W	L	Metal	Bacterial	N	Y	3	4	N
4	1973	49	M	W	L	Fingernail	Bacterial	N	Y	48	12	N
5	1974	11	M	W	R	Metal	Fungal	N	N	2	3	N
6	1976	8	M	W	R	None	Bacterial	N	Y	3	9.5	N
7	1976	24	M	H	R	Proptosis	Sterile	N	N	5	2.5	N
8	1977	8	M	W	L	Plant	Bacterial	Y	Y	9	5	N
9	1977	61	M	W	R	Sawdust	Bacterial	Y	Y	10	7.5	N
10	1977	63	M	W	L	Contact lens	Bacterial	Y	Y	14	9	N
11	1979	65	M	B	R	ND	Bacterial	N	Y	10	10	Y
12	1979	50	M	W	L	Chemical	Toxic	Y	Y	24	8	N
13	1981	50	M	H	R	Metal	Bacterial	N	Y	3	9	N
14	1981	52	M	W	L	Wood	Bacterial	N	Y	56	2	N
15	1982	51	M	B	L	Plant	Bacterial	N	Y	6	2	N
16	1984	6	F	W	L	Plant	Sterile	Y	Y	14	9	N
17	1987	26	M	B	R	Metal	Bacterial	Y	Y	3	8	N
18	1987	57	M	W	L	Dirt	Herpetic	N	Y	67	7	N
19	1987	30	M	H	R	Plant	Fungal	N	N	12	4	N
20	1988	10	M	W	R	Firecracker	Bacterial	N	Y	1	3.5	N
21	1988	57	M	W	L	Plant	Bacterial	Y	Y	10	5	N
22	1990	50	M	W	L	Radial keratotomy	Bacterial	N	Y	7	7	N
23	1990	35	M	W	L	Metal	Bacterial	Y	Y	4	9.5	Y
24	1992	62	M	W	R	Plant	Bacterial	N	Y	3	1	N
25	1992	15	M	W	L	Metal	Sterile	Y	N	2	2	Y
26	1993	60	M	W	L	Dirt	Herpetic	N	Y	10	8	N
27	1994	46	F	W	L	Metal	Bacterial	N	Y	12	9	N
28	1996	75	M	W	L	Sand	Fungal	N	N	2	16	N
29	1996	45	M	W	R	Wood	Bacterial	Y	Y	7	3.5	N
30	1998	69	M	W	R	Plant	Sterile	Y	Y	39	3	N
31	1998	33	M	H	L	Plant	Bacterial	N	Y	4	5	N
32	1999	71	M	W	L	Dirt	Bacterial	N	Y	11	27	Y

B, black; H, Hispanic; N, no; ND, not determined; Y, yes; W, white.

median of 2 days passed before patients obtained initial eye care following trauma or symptom onset, and a median of 7 days had elapsed when antifungal therapy was started. Patients with plant or dirt trauma were 4.8 (95% CI, 1.07 to 21.4) times more likely to have a delayed diagnosis greater than 1 week after onset ($P = .04$). Before starting antifungal therapy, 24 patients (75%) were treated with one or more topical antibacterial agents, and 11 (34%) used a topical corticosteroid.

At the time of establishing fungal keratitis, the average ± SD area of the corneal infiltrate was 7 mm^2 ± 5 mm^2. Four (12.5%) eyes had a hypopyon. Infection usually involved the center or lower half of the cornea (Fig 4). Early involvement typically presented as a feathery, superficial stromal infiltration with an epithelial defect (Fig 5). Two patients had brown pigmentation in the central portion of the infiltrate (Fig 6), although rust was a possibility in one. After the infection was established for longer than 1 week, focal necrotizing inflammation tended to obscure the velvety edges (Fig 7). Chronic forms of *Curvularia* keratitis varied from suppurative ulceration to smoldering inflammation that seemed to be partially

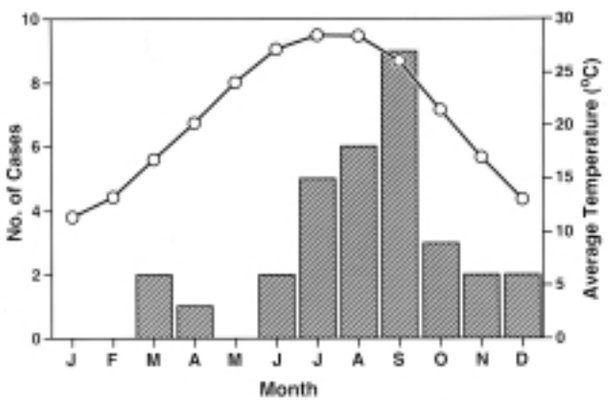


FIGURE 3
Seasonal distribution of onset of *Curvularia* keratitis (bars), compared to average temperatures of upper Texas coast (circles).

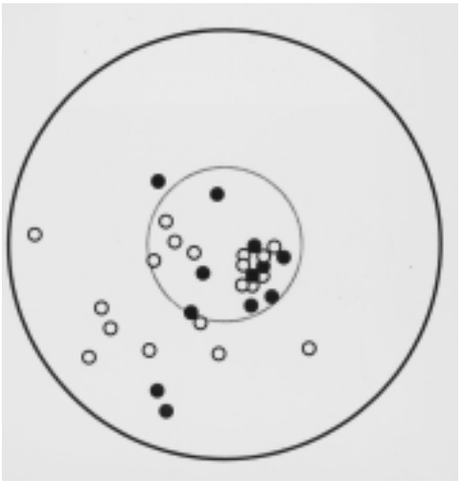


FIGURE 4
Topographic locations of stromal infiltrates' centers from patients with *Curvularia* keratitis. (Closed circles, right eyes; open circles, left eyes.)

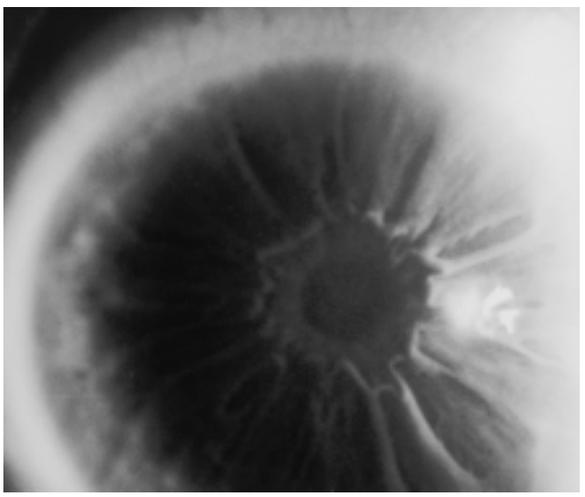


FIGURE 5B
Case 24. *Curvularia senegalensis* keratitis 3 days after injury to cornea while patient was using a lawn trimmer.

suppressed by topical antibacterial agents (Fig 8).

The median duration of topical antifungal therapy was 31.5 days (Table II), and the mean duration was 40 days. Topical natamycin 5% suspension was used in all but 1 patient who was treated with topical miconazole 1%. Adjunctive therapy included a second topical antifungal agent in 4 patients (3 with amphotericin B and 1 with miconazole) and oral antifungal therapy in 7 patients (4 with ketoconazole and 3 with fluconazole). A topical corticosteroid was used during antifungal therapy in 4 patients.

Corneal surgery was performed in 6 (19%) of the patients. A superficial keratectomy was performed on 3 eyes with an elevated or sequestered fibroinflammatory mass (Fig 9). Other complications included descemetocele (Fig 10) and recrudescent infection from inadequate

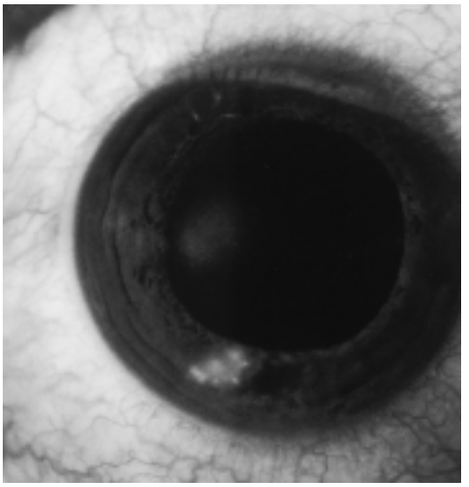


FIGURE 5A
Case 7. *Curvularia pallescens* keratitis 5 days after onset of symptoms attributed to exposure from proptosis. (Compare Fig 5b-Fig 5g, all early infections occuring within first week of onset).

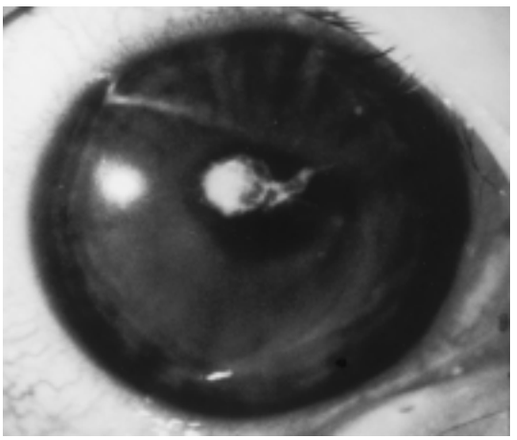


FIGURE 5C
Case 6. *Curvularia* keratitis 3 days after patient awoke with eye pain.

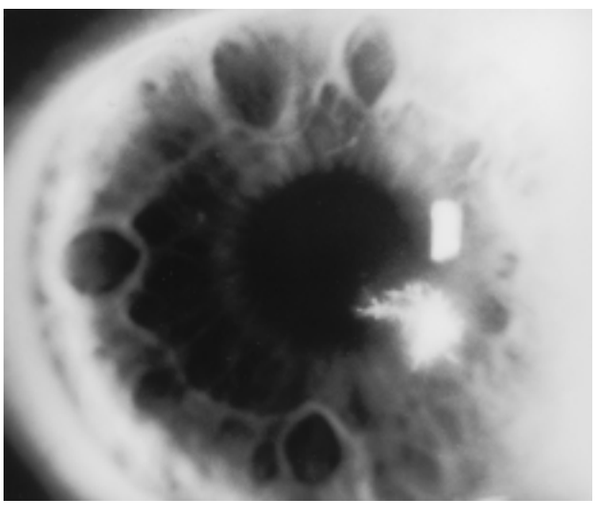


FIGURE 5D
Case 29. One week after onset of *Curvularia* keratitis due to a construction accident.

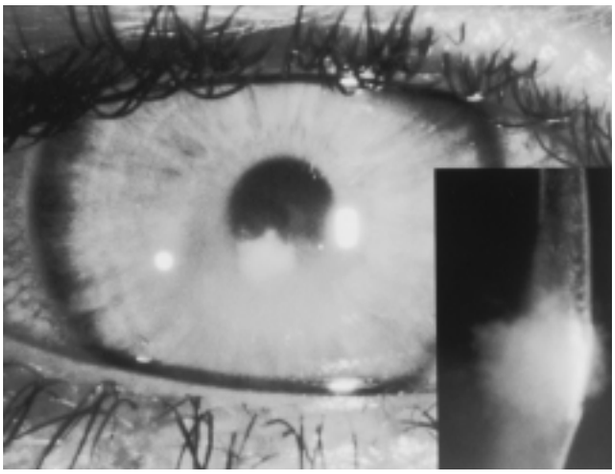


FIGURE 5E
Case 20. *Curvularia senegalensis* keratitis 2 days after firecracker injury.

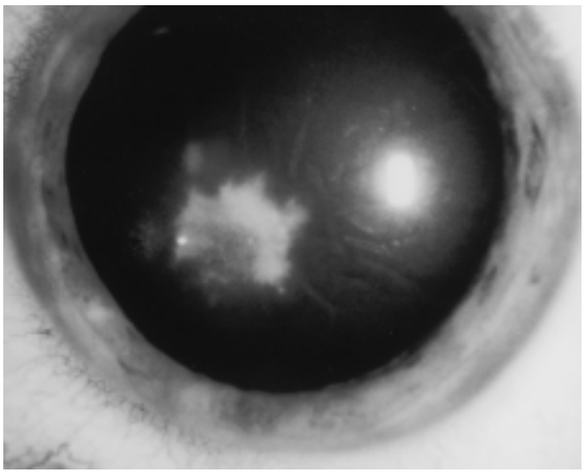


FIGURE 5F
Case 5. *Curvularia* keratitis 2 days after a screwdriver injury.

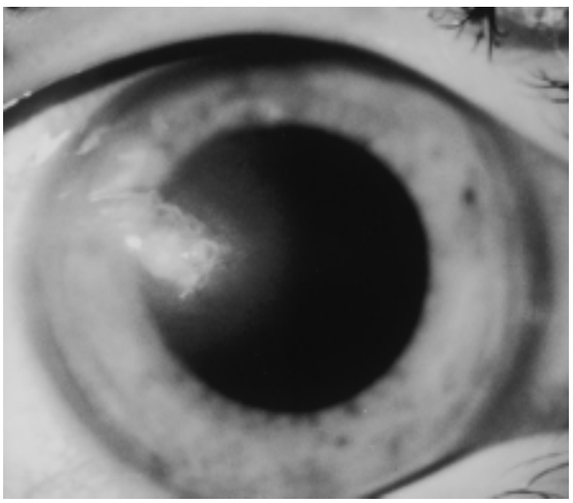


FIGURE 5G
Case 23. *Curvularia senegalensis* keratitis 4 days after a corneal metallic foreign-body injury that happened while patient was repairing a sewer.

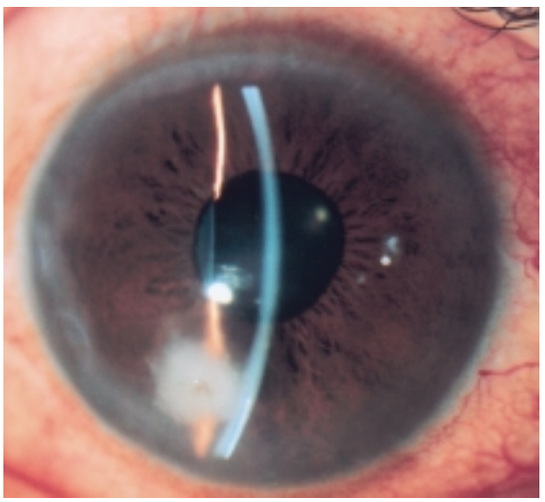


FIGURE 6A
Case 13. Superficial stromal pigment in center of a focal infiltrate, 3 days after a corneal metallic foreign-body injury.

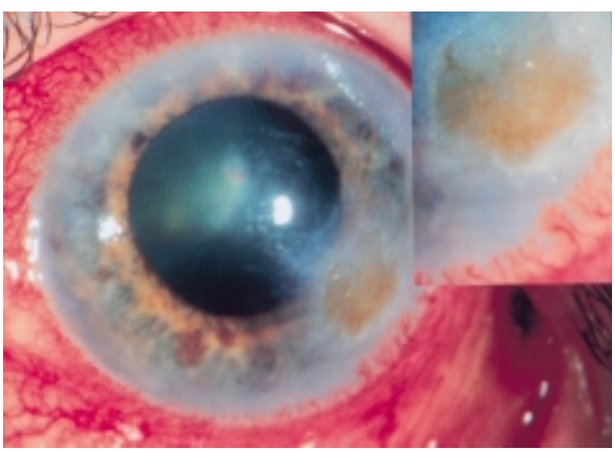


FIGURE 6B
Case 28. Brown pigmentation and persistent epithelial defect 3 weeks after patient got sand in eye.

FIGURE 7A
Case 10. *Curvularia lunata* keratitis after 2 weeks of symptoms, treated for a soft contact lens–related infiltrate with fluorometholone, gentamicin, neomycin-polymyxin B, and chloramphenicol eyedrops. (Compare Fig 7b-Fig 5d, all established infections occuring 10 to 14 days after onset).

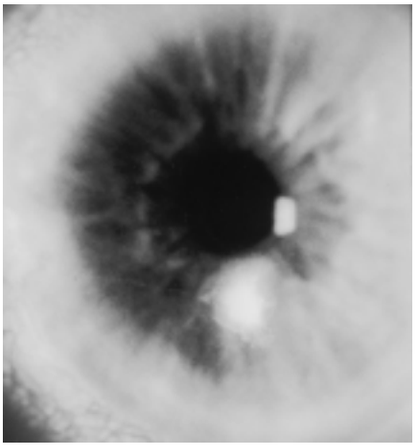


FIGURE 7B

Case 26. *Curvularia lunata* keratitis 10 days after onset, treated with trifluridine and tobramycin for presumed herpes simplex virus keratitis.

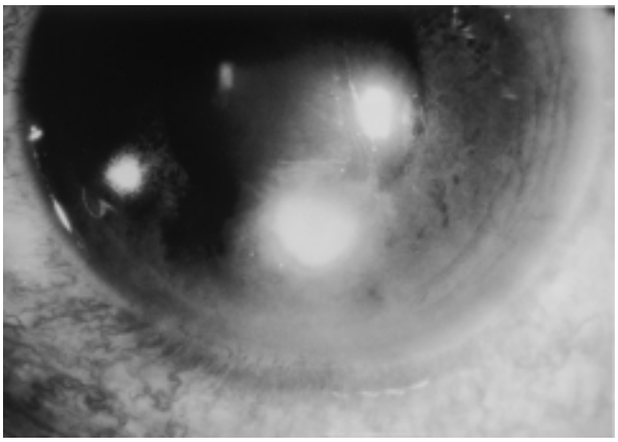


FIGURE 7C

Case 21. *Curvularia senegalensis* keratitis 10 days after a corneal abrasion caused by a lawn mower and treated with tobramycin-dexamethasone solution.

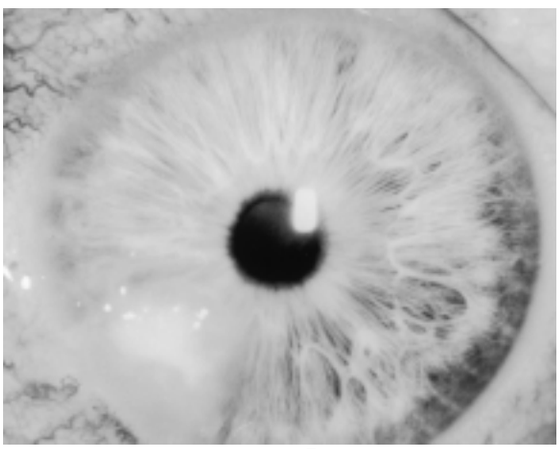


FIGURE 7D

Case 27. *Curvularia lunata* keratitis 12 days after abrading the cornea with a rusted wire and treated with ciprofloxacin and tobramycin eyedrops.

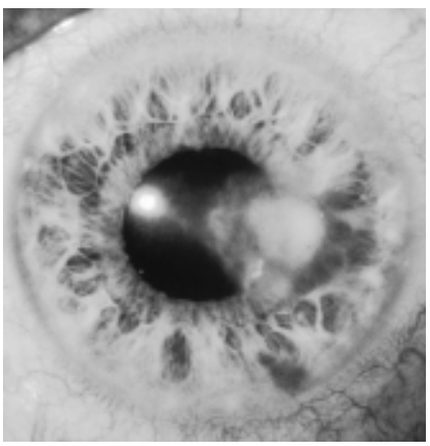


FIGURE 8A

Case 4. *Curvularia pallescens* keratitis 7 weeks after a fingernail-induced corneal injury. (Compare Fig 8b and Fig 8c, other chronic infections).

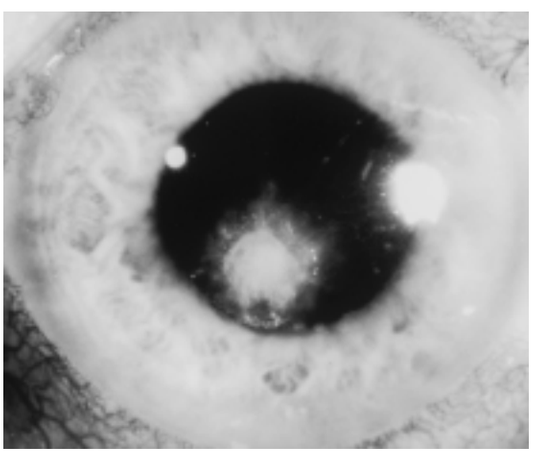


FIGURE 8B

Case 30. *Curvularia lunata* keratitis 5 weeks after a corneal injury that happened while patient was using a lawn mower. Infection was treated with neomycin-polymyxin B–dexamethasone solution.

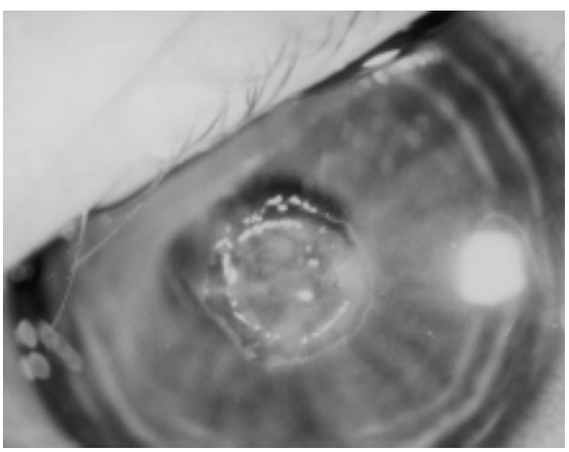


FIGURE 8C

Case 16. *Curvularia prasadii* keratitis 2 weeks after patient scratched cornea on a yucca leaf; corneal signs were apparently suppressed by neomycin-dexamethasone eyedrops.

TABLE II: MICROBIOLOGIC AND TREATMENT RESULTS OF CASES OF *CURVULARIA* KERATITIS

CASE	HYPHAE ON SMEAR	CULTURE	OTHER CORNEAL ISOLATES	DAYS OF NATAMYCIN THERAPY	OTHER ANTIFUNGAL THERAPY	SURGERY	FINAL VISUAL ACUITY
1	N	*C senegalensis*	-	ND	N	N	ND
2	Y	*C lunata*	*Bacillus badius*	22	N	N	20/25
3	Y	*C senegalensis*	*Staphylococcus epidermidis, Geotrichum candidum*	17	N	N	20/20
4	Y	*C pallescens*	*S epidermidis*	33	Amphotericin B	N	20/25
5	Y	*Curvularia* sp	-	21	N	N	20/20
6	N	*Curvularia* sp	-	11	N	N	20/25
7	N	*C pallescens*	*S epidermidis*	ND	N	N	20/20
8	N	*Curvularia* sp	-	40	Amphotericin B	N	20/30
9	Y	*C senegalensis*	-	48*	Miconazole	N	20/20
10	Y	*C lunata*	-	60	N	N	20/20
11	Y	*C lunata* var *aeria*	*S epidermidis, Peptostreptococcus micros, Propionibacterium acnes*	ND	N	Keratectomy	20/50
12	Y	*C prasadii*	-	115	N	PKP	20/40
13	Y	*C senegalensis*	*P acnes*	23	N	N	20/20
14	Y	*C lunata*	*S epidermidis*	75	N	Keratectomy	20/20
15	Y	*C senegalensis*	-	14	N	N	20/40
16	Y	*C prasadii*	*Streptococcus morbillorum*	24	N	N	ND
17	Y	*C pallescens*	-	42	Amphotericin B	N	20/30
18	Y	*C senegalensis*	-	79	Miconazole, oral ketoconazole	Keratectomy	20/20
19	Y	*C pallescens*	-	50	Oral ketoconazole		20/30
20	Y	*C senegalensis*	-	19	N	N	20/70
21	Y	*C senegalensis*	-	47	N	N	20/40
22	Y	*C senegalensis*	*P acnes*	39	N	N	20/20
23	N	*C senegalensis*	*P acnes*	86	Oral ketoconazole	N	20/20
24	N	*C senegalensis*	-	30	N	N	20/20
25	Y	*C lunata*	-	12	Oral ketoconazole	PKP	20/400
26	Y	*C lunata*	*P acnes*	ND	N	N	20/30
27	Y	*C lunata*	-	78	Oral fluconazole	N	20/20
28	Y	*Curvularia* sp	-	35	Oral fluconazole	N	20/100
29	Y	*Curvularia* sp	-	24	N	N	20/30
30	N	*C lunata*	-	25	N	N	20/30
31	Y	*C lunata*	-	21	N	N	20/30
32	Y	*C lunata* var *aeria*	-	29	Oral fluconazole	PKP	20/125

N, no; ND, not determined; PKP, penetrating keratoplasty; Y, yes.
*Only topical miconazole

therapy (Fig 11). Three patients underwent penetrating keratoplasty. Histopathological examination of 2 of these corneal buttons showed branching fungal elements (Fig 12). Despite these occurrences, 25 (78%) of all cases achieved visual acuity of 20/40 or better (Fig 13).

Logistic regression models assessing possible associations between initial clinical findings and either visual outcome or treatment duration are summarized in Table III. Multivariable modeling, selecting variables based on the likelihood ratio test, left only the presence of hypopyon in the final model with the visual acuity outcome. A similar model-building algorithm left only treatment delay in the final model with the treatment duration outcome. Linear regression showed that, on average, patients experiencing a delay in diagnosis greater than 7 days had 1.95 (95% CI, 1.78 to 2.37) times the duration of topical antifungal treatment than those diagnosed within 1 week of onset (P = .005), even after accounting for prior corneal trauma, prior corticosteroid therapy, infiltrate size, and hypopyon. Patients with a diagnostic delay greater than 1 week were treated for an average of 26 days (95% CI, 9 to 44 days) longer than those with a more rapid diagnosis.

Outcome was not convincingly correlated with natamycin's MIC (P = .6, using a breakpoint of 4 μg/mL) or MFC (P = .3, using a breakpoint of 16 μg/mL). The duration of topical natamycin was also not associated with

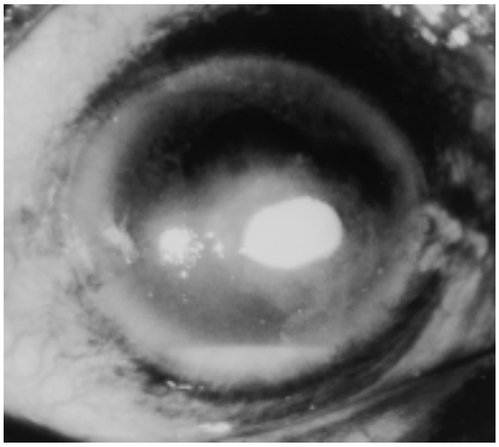


FIGURE 9A

Case 11. *Curvularia lunata* keratitis with dense white lesion extending above corneal surface.

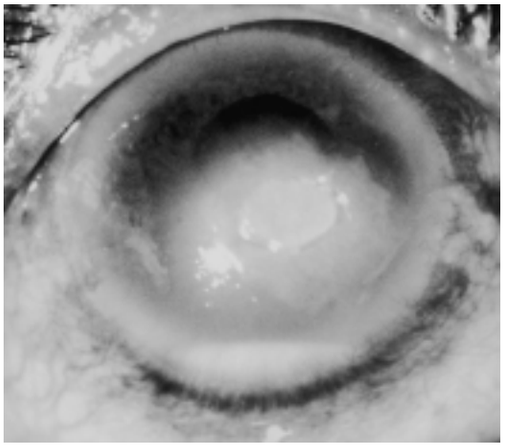


FIGURE 9B

Case 11. Three days after superficial keratectomy. (Compare Fig 9a).

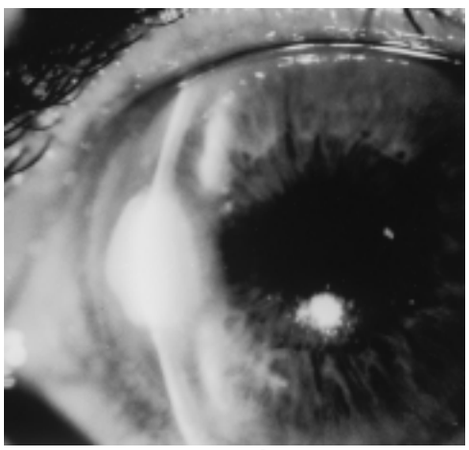


FIGURE 9C

Case 14. *Curvularia lunata* keratitis 8 weeks after onset with inflammatory outgrowth.

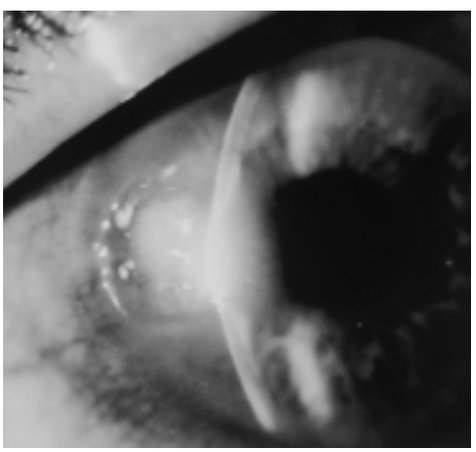
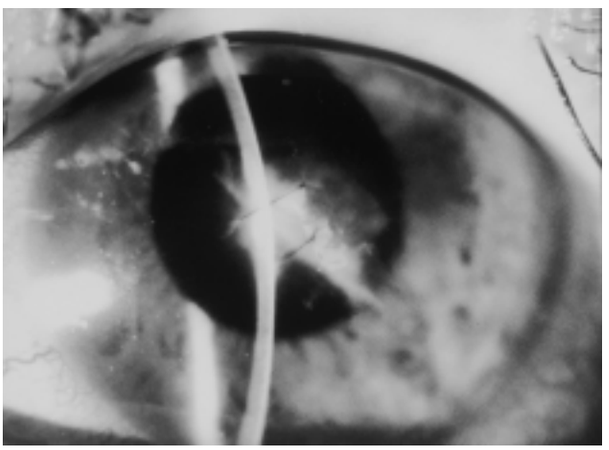


FIGURE 9D

Case 14. Superficial keratectomy performed 11 weeks after onset (compare Fig 9C). Corneal biopsy contained hyphae.



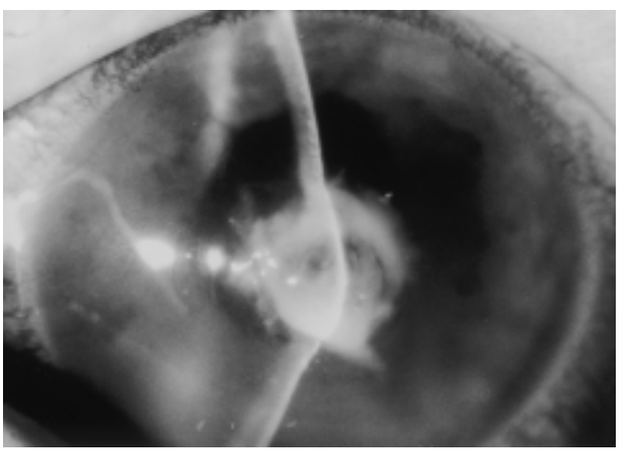


FIGURE 10

Case 25. Progressive ulceration. Top, *Curvularia lunata* keratitis 2 days after onset of a corneal suture abscess, occurring 2 months after penetrating corneal injury due to hammering nail into a tree. Bottom, Descemetocele 1 week later, after topical corticosteroid treatment every 2 hours was stopped and topical natamycin therapy was started (MIC = 2 μg/mL).

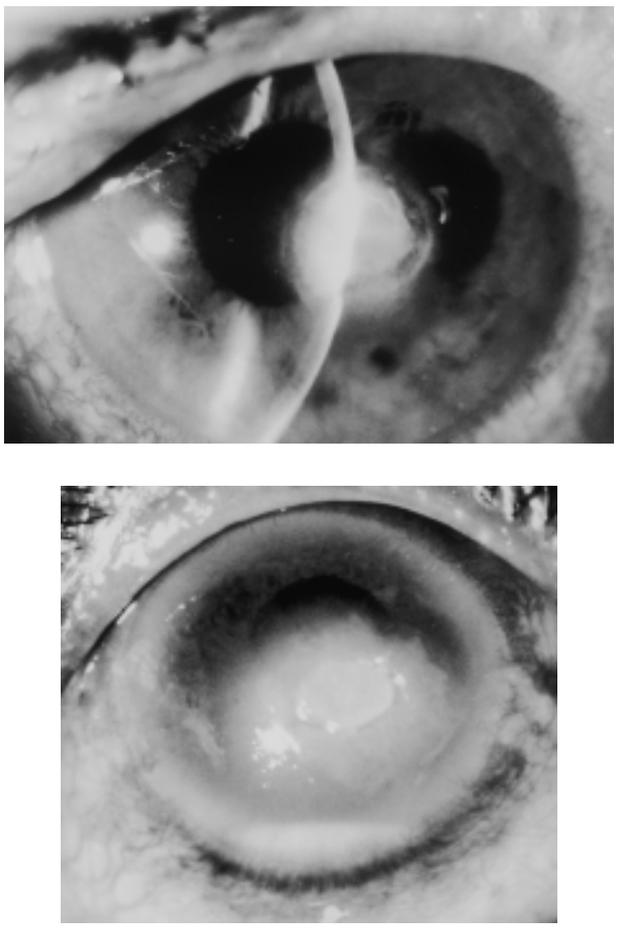


FIGURE 11

Case 18. Recrudescent inflammation after premature discontinuation of antifungal therapy. Top, *C senegalensis* keratitis at onset of antifungal therapy. Patient had scratched eye 2 months previously but was treated for herpes simplex virus dendritic keratitis, then stromal keratitis. Bottom, After near-resolution of inflammation with 6 weeks of topical natamycin therapy (MIC = 1 μg/mL), corneal infiltrate recurred 3 weeks after treatment was stopped. After 3 more weeks of natamycin, superficial keratectomy removed sequestered inflammation.

natamycin's MIC (P = .6) or MFC (P = .3), using similar breakpoints to define susceptibility. The different *Curvularia* species were not correlated with clinical severity, as assessed by infiltrate area or hypopyon, although the duration of topical therapy was significantly longer for patients with *C prasadii* infection (P = .01). The use of an adjunctive oral antifungal agent was not associated with visual outcome (P = .08) or duration of topical antifungal therapy (P = .14), but oral antifungals were used 5.5 (95% CI, 0.8 to 37.6) times more often among those with a poorer visual outcome and 2.3 (95% CI, 0.3 to 14.2) times more often in patients treated topically for more than 30 days.

MYCOLOGICAL FINDINGS

Dematiaceous hyphomycetes accounted for 22% of our fungal corneal isolates, and one third of these pigmented

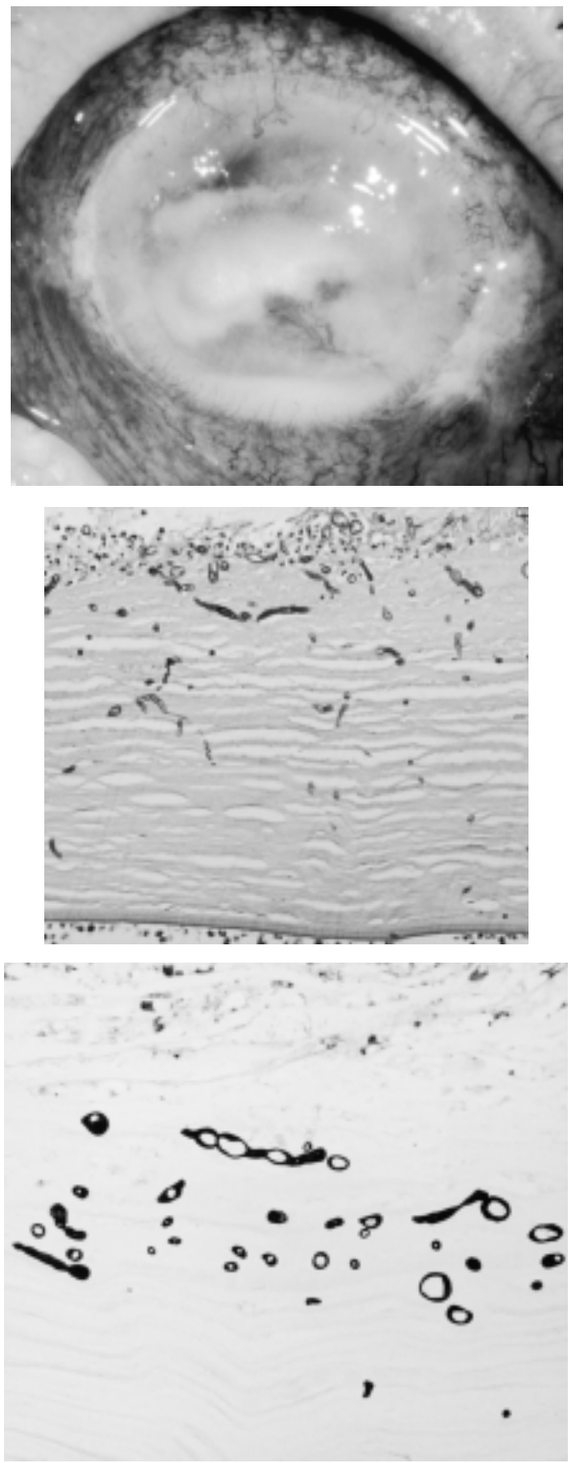


FIGURE 12

Case 32. Progressive *Curvularia* keratitis treated by therapeutic keratoplasty. Top, *Curvularia lunata* keratitis 10 days following corneal injury sustained while patient was cleaning his attic. Reconstructive keratoplasty occurred 1 week later. Center, Prominent neutrophilic infiltrate in stroma and anterior chamber, with PAS-positive filamentous fungi amongst necrotic lamellae (periodic acid–Schiff, x64). Bottom, Branching, septate filaments rooting into stroma and chlamydospores budding in superficial cornea (Gomori methanamine silver, x100).

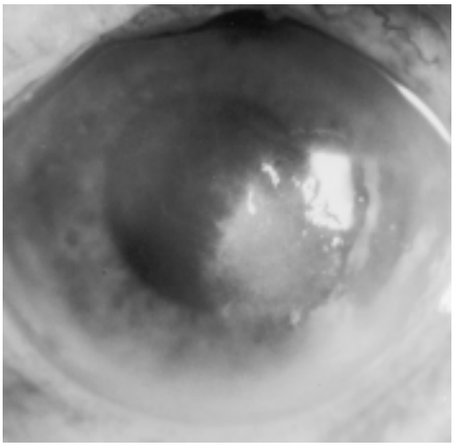


FIGURE 13A
Case 3. *Curvularia senegalensis* keratitis 3 days after corneal injury.

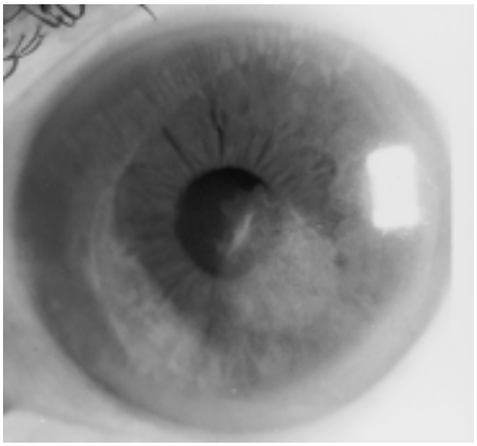


FIGURE 13B
Case 3. Four months later (compare Fig 13A) with faint corneal scar and 20/20 visual acuity.

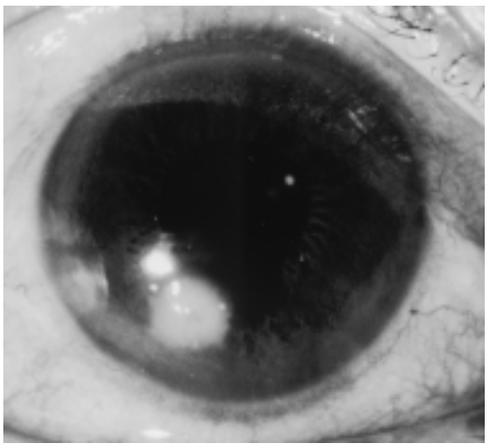


FIGURE 13C
Case 13. *Curvularia senegalensis* 3 days after onset.

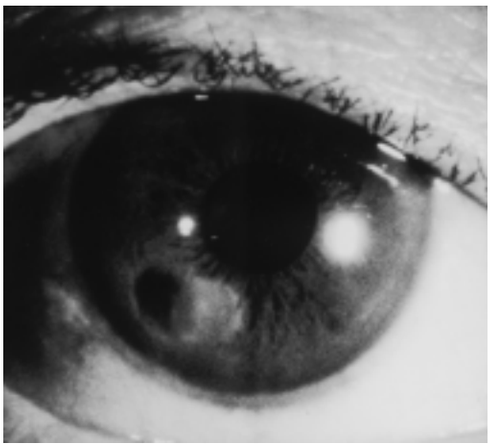


FIGURE 13D
Case 13. One month later (compare Fig 13C) with outcome of 20/20 visual acuity.

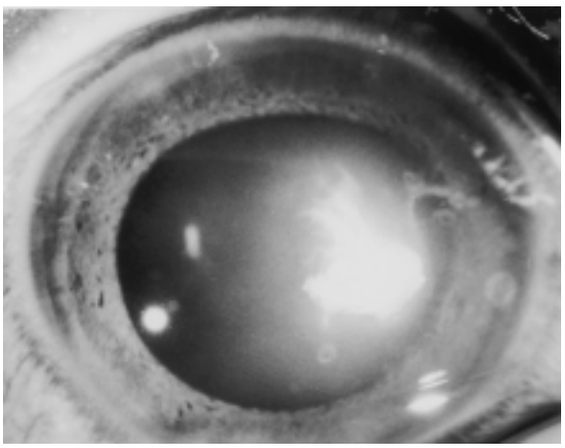


FIGURE 13E
Case 17. *Curvularia pallescens* keratitis 3 days after corneal injury.

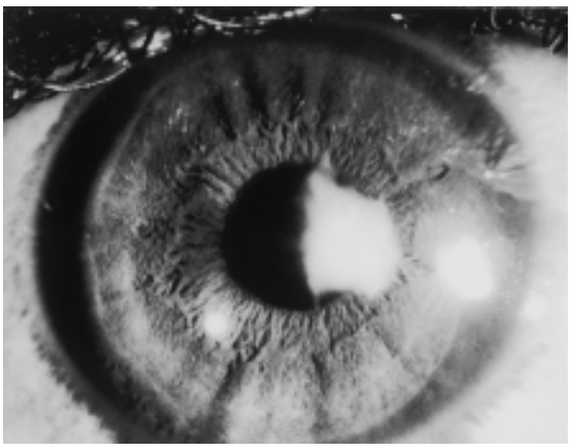


FIGURE 13F
Case 17. Three months later (compare Fig 13E) with outcome of 20/30 visual acuity.

TABLE III: UNIVARIABLE ASSOCIATIONS WITH POOR VISUAL OUTCOME AND PROLONGED TREATMENT DURATION

CHARACTERISTIC	FINAL VISION WORSE THAN 20/50 OR CORNEAL SURGERY		DURATION OF TOPICAL ANTIFUNGAL THERAPY > 30 DAYS	
	ODDS RATIO (95% CONFIDENCE INTERVAL)	*P* VALUE	ODDS RATIO (95% CONFIDENCE INTERVAL)	*P* VALUE
Age ≥ 50 yr	2.33 (0.36, 15.05)	.4	1.67 (0.41, 6.82)	.5
Plant or dirt trauma	0.50 (0.08, 3.22)	.5	0.80 (0.20, 3.25)	.8
Treatment delay > 7 days	1.17 (0.20, 6.89)	.9	7.33 (1.47, 36.66)	.015
Topical corticosteroid between onset and diagnosis	0.94 (0.14, 6.19)	.9	1.59 (0.36, 7.12)	.5
Topical antibiotic between onset and diagnosis	0.60 (0.09, 4.12)	.6	0.71 (0.14, 3.66)	.7
Stromal infiltrate > 9 mm^2	7.67 (1.04, 56.77)	.05	2.25 (0.54, 9.45)	.3
Presence of hypopyon	25.0 (1.93, 324)	.01	0.75 (0.09, 6.11)	.8

isolates were *Curvularia*. *Curvularia* was the fourth most common isolate among our cases of fungal keratitis, following *Candida*, *Fusarium*, and *Aspergillus*. *Curvularia* accounted for 8% of 727 cases of human keratomycosis and for 4% of 95 specimens from oculomycoses in dogs, horses, and other animals processed by our laboratory over the last 30 years.

Hyphae were detected on stained smears of initial corneal scrapings from 25 (78%) of the 32 culture-confirmed patients with *Curvularia* keratitis in this series. Hyphal fragments were seen on 21 (72%) of gram-stained smears from 29 different patients, 6 (75%) of 8 acridine orange smears, 7 (70%) of 10 Giemsa smears, and 5 (83%) of 6 smears stained with calcofluor white. No significant difference was found among these 4 stains ($\chi^2 = 0.4$, $df = 3$). Fungal DNA was detected from 4 corneal isolates (including cases 23, 30, and 31) amplified by PCR (Fig 14).

Fungal growth was first detected at a median of 2 days for both blood and chocolate agar plates, 4 days for Sabouraud agar, and 5 days for BHI (Table IV). Of 23 cases where comparative information was recorded, fungal growth was detected on the blood or chocolate agar plates on the same day as on the Sabouraud or BHI media in 5 cases. In 10 cases, fungi grew more rapidly on blood and chocolate agars, appearing an average of 3 days (range, 1 to 6 days) before growth occurred on Sabouraud or BHI media. Fungal growth was detected on blood or chocolate agar plates but not on the Sabouraud agar plate or in BHI in 5 cases (2 *C lunata*, 1 *C senegalensis*, 1 *C prasadii*, and 1 nonspeciated isolate). Fungi were found on Sabouraud or BHI media but not on blood or chocolate agar plates in 4 cases (2 *C pallescens*, 1 *C lunata*, and 1 *C senegalensis*). Besides the *Curvularia* isolate, 11 (34%) of the cases had 1 or more other microorganisms isolated from the corneal scrapings (Table II). *Staphylococcus epidermidis* and *Propionobacterium acnes*

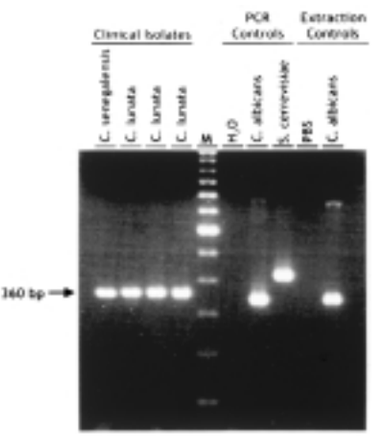


FIGURE 14

Fungal molecular analysis, electrophoretically analyzed on an agarose gel stained with ethidium bromide. Polymerase chain reaction (PCR) products of corneal cultures of 1 *Curvularia senegalensis* isolate (case 23) and 3 *Curvularia lunata* isolates (including cases 30 and 31) amplified consistently at predicted PCR product size of approximately 360 base pairs (bp). Other lanes show a base-pair ladder of size markers (M) and positive and negative controls for PCR reaction and extraction.

were the most common coisolates, although 1 case each of *Bacillus badius*, *Streptococcus morbillorum*, and *Geotrichum candidum* were found.

Curvularia species included *C senegalensis* (11 cases), *C lunata* (10 cases), *C pallescens* (4 cases), and *C prasadii* (2 cases). Five isolates were not speciated. Besides these 32 cases, our laboratory also identified *Curvularia* from 11 other patients with fungal keratitis using specimens sent to us by other treating ophthalmologists, comprising *C senegalensis* (3), *C lunata* (3), *C inæqualis* (1), *C leonensis* (1), and 3 nonspeciated strains.

The susceptibility pattern of the 14 tested isolates is shown in Table V. All of the *Curvularia* isolates were inhibited by ≤ 4 μg/mL natamycin, 86% by ≤ 1 μg/mL

TABLE IV: FUNGAL GROWTH FROM CORNEAL SCRAPINGS INOCULATED DIRECTLY ONTO CULTURE MEDIA

MEDIUM	MEDIAN DAYS (RANGE) OF FIRST DETECTABLE FUNGAL GROWTH	NO. WITH DETECTABLE FUNGAL GROWTH (NO. INOCULATED)	NO. OF CASES SHOWING GROWTH BEFORE OTHER SETS OF MEDIA*
Blood agar plate	2 (1 – 4)	17 (22)	15
Chocolate agar plate	2 (1 – 4)	19 (23)	15
Thioglycolate broth	3	2 (6)	0
Schaedler or Brucella agar plate	6 (1 – 7)	4 (5)	0
Sabouraud agar plate	4 (1 – 8)	15 (22)	4
Brain-heart infusion broth	5 (1 – 12)	12 (13)	4

*Fungal growth was identified on all media on same day for 4 specimens.

amphotericin B, 100% by ≤ 8 μg/mL miconazole or ketoconazole, 86% by ≤ .5 μg/mL itraconazole, and only 8% by ≤ 16 μg/mL flucytosine. All species appeared similar in their susceptibility pattern (Table VI).

Our laboratory's initial attempt at establishing an experimental animal model of *Curvularia* keratitis was unsuccessful. Faint corneal haze was noted in a few animals on the first day following scarification. With periodic observation over 1 month, none of the inoculated mouse eyes developed clinical, histological, or molecular evidence of fungal keratitis.

DISCUSSION

Human mycoses are caused by many mitosporic filamentous fungi. Most are classed as deuteromycetes, and these imperfect fungi include nonpigmented (hyaline or moniliaceous) and pigmented (dematiaceous) groups. The histopathological recognition of dematiaceous hyphomycetes is based on seeing tissue invasion by pigmented hyphae, a condition sometimes called phæohyphomycosis.[95] *Curvularia* is one of several genera of these "black fungi."[96]

EPIDEMIOLOGY

Dematiaceous molds live and linger in the soil[97] and on plants[98] in warm climates. Probably because of their widespread presence in the subtropical environment, dematiaceous hyphomycetes caused 22% of our cases of fungal keratitis and 16% to 19% in other large series.[36,42] *Curvularia* is the most common dematiaceous fungal corneal isolate[3,36,41,44,46,55,65] and accounts for 4% to 9% of all fungi isolated from patients with mycotic keratitis in hot zones.[41,46,65,70]

One hundred ninety cases of *Curvularia* keratitis have been previously reported (Table VII). We identified 43 additional patients with corneal curvulariosis, including 32 treated at and followed up by our institute. The numbers of reported cases progressively increased during the last half of the 20th century (Fig 15). One fourth of the reports and one fourth of the total number of previously

TABLE V: SUSCEPTIBILITY OF *CURVULARIA* CORNEAL ISOLATES

ANTIFUNGAL	MINIMAL INHIBITORY CONCENTRATION (MIC)				MINIMAL FUNGICIDAL CONCENTRATION (MFC)			
	NO. TESTED	MIC RANGE	MIC_{50} (μG/ML)	MIC_{90} (μG/ML)	NO. TESTED	MFC RANGE	MFC_{50} (μG/ML)	MFC_{90} (μG/ML)
Natamycin	14	1 – 4	1	2	7	1 - >32	16	16
Amphotericin B	14	≤0.125 – 4	0.5	1	7	0.5 - >32	8	32
Clotrimazole	11	<0.25 – 8	1	4	7	1 - >32	8	>32
Miconazole	14	<0.25 – 2	1	1	7	0.5 - >32	4	32
Econazole	12	0.125 – 1	0.25	0.5	7	<0.25 – 32	1	16
Ketoconazole	9	<0.25 – 4	0.5	2	4	0.25 – 16	8	16
Butaconazole	6	≤0.25 – 1	0.5	1	1	0.5	0.5	-
Itraconazole	7	≤0.25 – 1	0.25	1	1	≤0.25	≤0.25	-
Fluconazole	3	>16	>16	>16	0	-	-	-
Saperconazole	3	≤0.06 – 0.5	0.125	0.5	0	-	-	-
Flucytosine	12	≤0.25 - >32	>32	>32	1	>32	>32	>32

TABLE VI: IN VITRO SUSCEPTIBILITIES (MIC_{50}) OF DIFFERENT *CURVULARIA* SPECIES

SPECIES	NO. TESTED ISOLATES	NATAMYCIN	AMPHOTERICIN B	MICONAZOLE	KETOCONAZOLE	ITRACONAZOLE
C lunata	4	1	0.5	1	2	1
C senegalensis	5	2	1	1	0.25	0.25
C pallescens	2	1	0.5	1	0.5	≤0.25
C prasadii	1	4	<0.25	1	0.5	-

reported patients came from the United States. Nearly half of the reports and two thirds of the cases were from India and surrounding Asian nations. Besides India (n=109) and the United States (n=89, including our series), other regions reporting patients with *Curvularia* keratitis were Asia (n=24; from Bangladesh, Taiwan, Thailand, Nepal, Sri Lanka, Korea, Singapore, and the Philippines), Africa (n=6; from South Africa and Ghana), South America (n=4; from Argentina, Brazil, Paraguay, and Venezuela), and the Middle East (n=1; from Israel).

We averaged one patient per year with *Curvularia* keratitis, and the annual experience can be higher at eye clinics in India.[36] Two thirds of our cases began during the summer, when *Curvularia* airborne spores peak along the Texas coast of the Gulf of Mexico.[99] *Curvularia* species are among the most prevalent fungal spores in the air in many torrid climes. The amount of aerial *Curvularia* varies seasonally,[70,100,101] rising during and just after the warm, wet months.

Practically all of our patients developed their fungal keratitis after trauma, one half with plants or dirt. Others have also found the injured cornea to be open to opportunistic fungal infection.[65] Previous reports that mentioned predisposing factors indicated trauma in 72% of patients with *Curvularia* keratitis (Table VII, data not shown). Lawn-tool injuries in our region are common grounds for ocular[30] and cutaneous[102] *Curvularia* infections. Outdoor occupational or recreational injury may explain why males accounted for 78% of all patients in our series and previous reports and why half were between 25 and 50 years of age (Fig 16). Children, however, are also at risk:[54] 16% of our patients were younger than 12 years of age.

Other predisposing factors include keratorefractive surgery,[29] corneal exposure, and climatic droplet keratopathy.[27,72] *Curvularia* keratitis is also a rare complication of soft contact lens wear,[82] possibly because this fungus is capable of contaminating contact lenses[82,103] and cosmetics.[104] *Curvularia* may be found on unwashed skin but colonizes less than 1% of normal human eyelids[105] and only 1% to 3% of healthy conjunctivæ.[70,106-108]

Curvularia keratitis has a slower course and less inflammation than some other fungal corneal infections.[34] Our patients often waited several days before seeking care, and half smoldered for more than a week before the diagnosis was made. An animal model of *Curvularia* keratitis also showed a gradually progressive evolution.[21] During its torpid course, fungal corneal infection allows an opportunity for bacteria, including staphylococci and anaerobes that are part of the ocular flora, to adhere to and possibly to infect the cornea. One third of our cases were polymicrobial infections, including one patient with polymycosis involving *Curvularia* and *Geotrichum*.

Similar to the 8% prevalence of *Curvularia* keratitis among human keratomycoses studied by our laboratory, we isolated *Curvularia* from 4% of all canine and equine

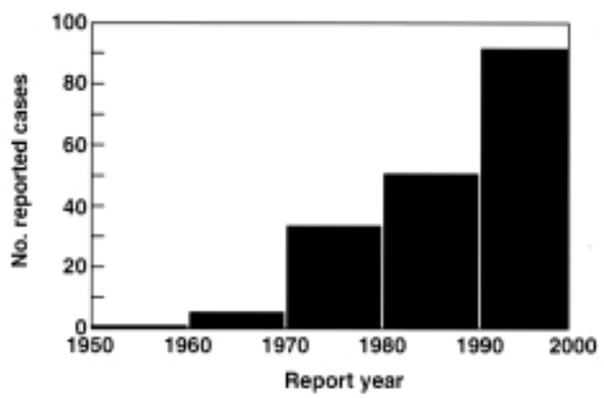


FIGURE 15
Time of literature publication of previously reported cases of *Curvularia* keratitis, by decade through the end of each reporting year.

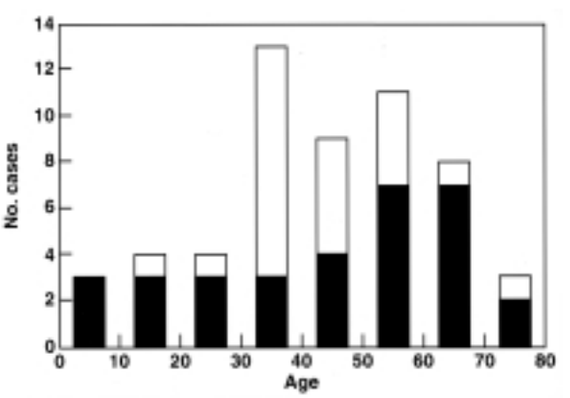


FIGURE 16
Age distribution of 32 patients with *Curvularia* keratitis in this series (black) and 23 previously reported cases with available demographic information (white).

TABLE VII: PREVIOUSLY REPORTED HUMAN CASES OF *CURVULARIA* KERATITIS

REPORTING AUTHOR, YEAR	LOCALE	ISOLATE	NO.
Agrawal et al, 1982[21]; Shukla et al, 1984[22]	India	*C lunata* var *aeria*	1
		C geniculata	1
Anderson et al, 1959[13]; Anderson and Chick, 1963[23]	North Carolina, USA	*C lunata*	1
Arora et al, 1983[24]	India	*Curvularia* sp	1
Berger et al, 1991[25]	California, USA	*C lunata*	1
Brook and Frazier, 1999[26]	Maryland, USA	*Curvularia* sp	1
Carmichael et al, 1985[27]	South Africa	*C lunata*	2
Chander and Sharma, 1994[28]	India	*Curvularia* sp	5
Chung et al, 2000[29]	Florida, USA	*Curvularia* sp	1
Clinch et al, 1992[30]; Clinch et al, 1994[31]	Louisiana, USA	*Curvularia* sp	2
Dasgupta et al, 1973[32]	India	*Curvularia* sp	4
Dorey et al, 1997[33]	Israel	*C lunata*	1
Dunlop et al, 1994[34]	Bangladesh	*C fallax*	7
		Curvularia sp	2
Fitzsimons and Peters, 1986[35]	South Africa	*Curvularia* sp	1
Garg et al, 2000[36]	India	*Curvularia* sp	20
Grover et al, 1975[37]	India	*Curvularia* sp	1
Guarro et al, 1999[38]	Brazil	*C senegalensis*	1
Hagan et al, 1995[39]	Ghana	*C fallax*	2
Imwidthaya, 1995[40]	Thailand	*Curvularia* sp	3
Jan et al, 1992[41]	Taiwan	*Curvularia* sp	4
Jones et al, 1969[2]; Forster et al, 1975[3]; Forster, 1994[42];	Florida, USA	*C senegalensis*	11
Forster and Rebell, 1975[43]; Liesegang and Forster, 1980[44]		*C verruculosa*	7
		C pallescens	1
		Curvularia sp	4
Kim et al, 2001[45]	Korea	*Curvularia* sp	1
Lakshmi et al, 1989[46]	India	*Curvularia* sp	18
Llamozas et al, 1966[47]	Venezuela	*C lunata*	1
Luque et al, 1986[48]	Argentina	*C lunata* var *aeria*	1
Mahajan, 1985[49]	India	*Curvularia* sp	9
Marcus et al, 1992[50]	South Africa	*C brachyspora*	1
Miño de Kaspar et al, 1991[51]	Paraguay	*Curvularia* sp	1
Nityananda et al, 1962[52]	Sri Lanka	*C lunata*	1
Nityananda et al, 1964[53]	Sri Lanka	*C geniculata*	1
Panda et al, 1997[54]	India	*Curvularia* sp	16
Poria et al, 1985[55]	India	*Curvularia* sp	1
Prasad and Neva, 1982[56]; Nema, 1991[57]	India	*C lunata*	3
Rahman et al, 1997[58]	India	*Curvularia* sp	2
Rajasekaran et al, 1988[59]; Thomas et al, 1987[60]; Thomas et al, 1986[61]	India	*C geniculata*	3
		Curvularia sp	5
Rajasekaran et al, 1987[62]; Thomas et al, 1988[63];			
Thomas and Rajasekaran, 1988[64]	India	*C geniculata*	1
Rosa et al, 1994[65]	Florida, USA	*C senegalensis*	5
		C verruculosa	1
		Curvularia sp	5
Salceda et al, 1969[66]; Salceda, 1973[67]; Salceda, 1973[68];			
Salceda et al, 1974[69]; Salceda, 1976[14]	Philippines	*Curvularia* sp	1
Sandhu and Randhawa, 1979[70]	India	*Curvularia* sp	5
Sanitato et al, 1984[71]	Louisiana, USA	*Curvularia* sp	1
Sridhar et al, 2000[72]	India	*C lunata*	1
Srinivasan et al, 1991[73]	India	*Curvularia* sp	3
Srinivasan et al, 1997[74]	India	*Curvularia* sp	5
Stern and Buttross, 1991[75]	Florida, USA	*Curvularia* sp	1
Sundaram et al, 1989[76]	India	*C lunata*	4
Upadhyay et al, 1991[77]; Upadhyay et al, 1992[78]	Nepal	*C prasadii*	2
Warren, 1964[79]; Georg, 1964[80]	Alabama, USA	*C geniculata*	1
Williams et al, 1991[81]	Bangladesh	*Curvularia* sp	1
Wilson et al, 1986[82]	Georgia, USA	*C lunata*	1
Wind and Polack, 1970[83]; Polack et al, 1971[84]; Polack, 1970[85]	Florida, USA	*C lunata*	1
Wong et al, 1997[86]; Wong et al, 1997[87]	Singapore	*Curvularia* sp	1
Wood and Turberville, 1985[88]	Tennessee, USA	*Curvularia* sp	1

fungal corneal infections submitted to us by veterinarians. Others have also reported *Curvularia* keratitis in dogs[109,110] and horses,[111] even elephants.[112] *Curvularia* is part of the conjunctival flora of domestic mammals,[113] but zootic keratomycosis is probably largely due to corneal trauma from vegetation.

MYCOLOGY

Gram, calcofluor white, and other stains of corneal scrapings were equally sensitive in detecting hyphal elements from our patients with *Curvularia* keratitis. Gomori's methanamine-silver helped visualize fungal biomass in corneal sections, and the Fontana-Masson silver stain can highlight melanin in dematiaceous fungal cell walls. A panfungal PCR offers a rapid diagnostic option.

Curvularia matures fairly rapidly on semisynthetic media,[114] generally showing detectable colonies at a median of 2 days on blood and chocolate agar plates and at 4 days on Sabouraud agar or brain-heart infusion. Other media also support *Curvularia*.[115] The optimal temperature for culturing many *Curvularia* species is around 28°C,[116,117] although growth occurs in both 25°C and 35°C incubators.[21] Colonies of the septate, brown hyphae vary from dark green to brownish black. Conidiophores produce multicelled conidia that measure 18 to 40 μ long, depending upon species. The mitospores' characteristic lunate arc comes from a central or penultimate conidial cell that tends to be larger, darker, and curved.

Approximately 40 species of *Curvularia* are known, including some conidial anamorphs of *Cochliobolus*.[118,119] *C lunata* and *C senegalensis* account for 60% of the recorded known species causing *Curvularia* keratitis in humans (Table VIII).

PATHOGENESIS

Our cohort provides some insight into how fungal infection develops and progresses in the cornea. A dry, superficial infiltrate with feathery borders was the typical appearance of curvularial infections involving the central and paracentral cornea. Peripheral corneal disease tended toward ulcerative suppuration. Eyes with more severe ocular inflammation, such as a hypopyon at the time of initial diagnosis, had a more complicated course and resulted in poorer vision.

The pathophysiology of *Curvularia* keratitis remains speculative. Fungal antigens are implicated in allergic sinusitis,[109] and one or more of these proteins could be involved in corneal inflammation. Fungal components that suppress the innate immune response and that interfere with human cytokines[120] could contribute to indolent infection.

Curvularia produces several mycotoxins, such as the curvularins, brefeldins, and radicinin, that are cytotoxic[121] and that have antiviral activity. Other toxins are anthroquinones, curvapallides, cytochalasins, neocoprogen, pectinases, pyrenocenes, spirostaphylotrichins, triticones, and zaragozic acid. *Curvularia* produces lipid phosphatase, galactosidase, glucosidase, endoglucanase, chloroperoxidase, and cellulases[122] and has pathways for metabolizing steroids. The roles of curvularial enzymes and other toxins in fungal keratitis have not yet been studied. What accounts for ocular virulence among *Curvularia* species is unknown.[123]

Melanin in the cell walls of dematiaceous hyphae and conidia resists killing and could be involved in pathogenicity. Although melanin production by dematiaceous fungi is downregulated at body temperature,[124] superficial corneal pigmentation was visible in 2 patients. Like others,[25,36,125] we found macroscopic pigmentation of ulcerative keratitis to be an uncommon but distinguishing sign of dematiaceous fungal infection.

The use of topical corticosteroids, inappropriately given before diagnosis in one third of our patients, may affect the course of *Curvularia* keratitis.[65] An animal model of *Curvularia* keratitis suggested that the severity of corneal infection was worsened by topical corticosteroids in the absence of antifungal therapy,[21] although we were unsuccessful in establishing a murine model even with systemic immunosuppression. After starting antifungal therapy, few of our patients were treated with corticosteroids because of uncertain safety, efficacy, and need.

MANAGEMENT

The optimal selection and duration of antifungal therapy could not be determined from this retrospective cohort study. Previous case reports have suggested that topical amphotericin B[13,50,79,86,88,126] or miconazole[35] is sometimes effective, and our susceptibility data showed good in vitro activity with these agents. Topical natamycin 5% suspension, first successfully used for *Curvularia* keratitis in

TABLE VIII: REPORTED HUMAN CORNEAL ISOLATES OF *CURVULARIA*

SPECIES	NO.
C lunata	32
C senegalensis	31
C fallax	9
C verruculosa	8
C geniculata	7
C pallescens	5
C prasadii	4
C brachyspora	1
C inæqualis	1
C leonensis	1

1970,[3,83] is a preferred therapy.[33]

Our experience corroborates the benefit of topical natamycin for corneal curvulariosis. On average, our patients were treated with one month of topical natamycin when the diagnosis was made soon after onset. A delay in starting natamycin prolonged the length of therapy. In vitro susceptibility testing showed all tested isolates to be susceptible to 4 μg/mL of natamycin or less, a concentration achievable in the ulcerated cornea by topical administration.[127] Natamycin (formerly, pimaricin) has agricultural applications and is an approved fungicide on cheese and other foods to prevent mold spoilage;[128] only minimal resistance has occurred despite widespread industrial use.[129] Ocular curvularial isolates acquired from the environment remain largely susceptible to natamycin.

Other compounds capable of inhibiting *Curvularia* range from biocides, such as polyhexamethylene biguanide[130] and chlorhexidine gluconate,[58] to the imidazoles.[131] Most isolates of *Curvularia* are sensitive to ketoconazole and itraconazole,[38] and an oral triazole antifungal agent can cure *Curvularia* keratitis even without topical therapy.[60,63] Voriconazole, a derivative of fluconazole, has good in vitro activity against *C lunata*[132,133] and may prove useful for treating patients with fungal keratitis.

Surgical management of *Curvularia* keratitis includes lamellar keratectomy,[71] conjunctival flap,[134] and therapeutic keratoplasty.[43,65] We treated fibroinflammatory outgrowth with superficial keratectomy, and 9% of our cases underwent corneal transplantation. We obtained medical or surgical cure in all patients, and 78% achieved vision of 20/40 or better.

An astute ophthalmologist once commented that "each fungus…can cause its own disease that may differ in its clinical features and prognosis from all others."[135] Our experience shows that *Curvularia* keratitis is a distinctive form of keratomycosis. By describing its characteristics and analyzing the clinical course, we aimed to learn more about how this fungus infects the cornea.

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DISCUSSION

DR JOHN D. GOTTSCH. Drs Wilhelmus and Jones are to be commended for their comprehensive review of a 30 year experience with *Curvalaria* keratitis. This is the largest series reported to date with this fungal corneal infection, a review all the more remarkable because the disease is less prevalent in the United States than in tropical countries. This series by Wilhelmus and Jones is possible because of their meticulous ocular microbiologic workups and data preservation over many years.

This study confirms several well known suspicions about this disease. First, keratomycosis is a rarely suspected diagnosis in presumed infectious keratitis. Only 5 of the patients were referred with fungal keratitis as the initial diagnostic impression. Secondly, fungal keratitis is more likely to develop with trauma, especially trauma that involves plants or soil. Only 3 patients did not have a history of trauma to the cornea, and half the patients in this study had sustained dirt or plant injuries. Thirdly, the disease is more likely to develop in hot humid environments. Seventy percent of cases in this study occurred along the Gulf Coast during the summer months. And lastly, topical steroid use likely facilitates the development of the disease as one third of the study patients had used topical steroids before referral.

What is most striking about this report is the recovery of vision that occurred in the majority of patients, with over half achieving 20/20-20/25 vision or better. Only 3 patients were 20/100 or worse, and only 3 required penetrating keratoplasties. This is in contrast to other literature reports concerning Curvalaris fungal infections which record many failed grafts, eviscerations and lost eyes. In this group of 32 patients no eyes were lost.

To what does Dr Wilhelmus owe the successful treatment of these difficult corneal infections? Certainly as the data demonstrated, a delay in initiating treatment led to a greater length of antifungal therapy. Two of the grafted patients had a treatment delay of greater than 10 days. As the data also show, a delay in treatment in general led to a larger area of stromal infiltrate and presumably a deeper, more entrenched infection. Thus, time to diagnosis and treatment is of the essence. Initial smears revealed hyphal elements from nearly 80% of the affected patients, and culture results confirmed the diagnosis within days in all cases. Thus a diagnosis could be established on the same day as presentation in most cases and within a week in the others. The median time to starting antifungal therapy was only 7 days. Thus effective antifungal therapy, mostly with natamycin, was begun early in the course of disease.

Had these patients been empirically treated with a topical fluoroquinolone only, as some have advocated for the treatment of presumed corneal ulcers, all these

infections would have progressively worsened. The incidence of fungal ulcers in India has been reported to be as high as 37% and in tropical climates, smears and cultures are routine in patients who present with signs of infectious keratitis.[1] The incidence of fungal disease in the United States is less.[2] Even though fungal ulcers are rare in our practices, should we as a routine matter of course perform smears and cultures on patients with presumed infectious keratitis, particularly those patients with risk factors for fungal keratitis such as trauma, warmer climates, and previous steroid use? Steroid use after initiation of antifungal therapy is also a controversial issue. I would also like to ask Dr Wilhelmus whether topical steroids should be considered in the management of fungal keratitis. Lastly, is there a role for cyclosporine as an antifungal and anti-inflammatory drug for keratomycotic infections as has been advocated by some investigators?

I congratulate Dr Wilhelmus for this large study of *Curvalaria* keratitis in the United States and providing us with a sound management strategy for this difficult disease.

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DR KIRK R. WILHELMUS. Dr Gottsch implies that we should treat fungal keratitis on a case-by-case basis. That's how some of us buy wine, and I agree that it's the best approach in external eye disease. Empirical diagnosis and hit-or-miss therapy are not the optimal ways to manage corneal infections. We attribute our successful treatment of of keratomycosis to a decision making plan that uses the capabilities of the microbiology laboratory.

We are entering the era of molecular ophthalmology. In his Jackson Memorial Lecture, Professor Barrie Jones intuited that "each fungus...is in search of its own specific effective management." With new rapid diagnostic assays, we will soon be able to identify microorganisms and to examine their susceptibilities on the day of diagnosis. We must be prepared to use this information by learning how each microbe correlates with clinical findings and with outcome.

We also need an improved classification scheme for fungal keratitis. Dematiaceous fungi cause a spectrum of diseases: mycetoma, an infection with aggregrated fungal granules; chromoblastomycosis, localized tissue inflammation with arrested fungal growth; and phæohyphomycosis, tissue invasion by pigmented fungi. As suggested by McGinnis and Ajello in 1985, mycotic keratitis caused by *Curvularia* and other dematiacious fungi is the ophthalmic counterpart to cutaneous phæohyphomycosis. Together, an ophthalmic pathologist and a clinical ophthalmologist could create an eye-specific nomenclature of ocular phæohyphomycosis, hyalohyphomycosis, candidiasis, and zygomycosis.

Let me now address the 3 main issues raised during the discussion: the risk factors of keratomycosis, its antifungal treatment, and the role of corticosteroids.

First, our experience shows that fungal keratitis mirrors nature, and we cannot be myopic when looking at the cornea. The recent proposal to use a coca-attacking strain of *Fusarium oxysporum* as a mycoherbicide in the war on drugs may mean that fungal eye disease could become more widespread. Harvey Cushing said: "A physician is obligated to consider more than a diseased organ, more even than the whole man–he must view the man in the world." We shouldn't be too surprised that many microorganisms are capable of infecting the eye or that case prevalence depends partly on the weather, geography, and human activity. To paraphrase TS Eliot, it is not our patient's eyes that are diseased, but the world we have to live in. Using PCR, our laboratory is finding that about one third of people have fungi in their normal flora. Dematiaceous fungi known to infect the cornea (including not only *Curvularia* but also *Bipolaris/Drechslera*, *Alternaria*, *Phialophora*, *Exserohilum*, *Fonsecæa*, *Exophiala*, *Aureobasidium*, *Cladosporium*, *Colletotrichum*, *Epicoccum*, *Humicola*, *Lasiodiplodia*, *Phoma* and *Wangiella*) are common in nature. Microorganisms that we know as corneal pathogens are, by and large, opportunists.

Secondly, we're fortunate to be the only specialty in medicine to use natamycin, an antifungal whose main niche is the food industry. This fungicide can reduce fungal growth on stored grain, but its most popular use is to prevent mold on cheese. After dipping or spraying cheese with Delvocid or a similar product at a concentration of 200 to 300 ppm, natamycin crystallizes on the rind but, being insoluble in water, does not leech into the paste. For example, natamycin works on Italian blue cheese by suppressing surface mold without interfering with *Penicillium gorgonzola* inside the punch holes. Mutant strains resistant to natamycin have little or no ergosterol in their cell membrane, so these fungi grow slowly and cannot survive in nature or on the eye. Natamycin remains our preferred therapy for most keratomycoses caused by dematiaceous and hyaline filamentous fungi. Yet, we still need better antifungal agents and easier ways to select them.

Finally, Dr Gottsch's questions about the role of corticosteroids and cyclosporine in fungal keratitis are intriguing but hard to answer. Like *Richard II*'s realm, the cornea is a "fortress built by Nature for herself against infection," with battalions of material and molecular defenses. But the cornea and her inflammatory

fortifications can self-destruct during microbial invasion. Although Drs Stern and O'Day wrote parallel articles 10 years ago that corticosteroids enhance fungal keratitis and are contraindicated, perhaps anti-inflammatory drugs do sometimes have an adjunctive role. Our laboratory and others have shown that cyclosporine has some intrinsic and synergistic antifungal activity and could prove worthwhile as a dual antifungal and anti-inflammatory agent. We have successfully used topical cyclosporine after reconstructive keratoplasty performed for fungal keratitis.

I appreciate the opportunity to present today. Many discoveries are yet to be made about fungal infections of the eye.