

Risk Factors for Treatment Outcome in Fungal Keratitis

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Purpose: To identify risk factors at diagnosis that can serve as prognostic indicators of primary treatment failure in cases of fungal keratitis.

Design: Prospective, nonrandomized, interventional, comparative study.

Participants: A total of 115 consecutive patients with fungal keratitis treated at one center during a 6-month period.

Methods: Patients with a microscopic corneal ulcer smear that was positive for fungus were enrolled and treated with 5% natamycin monotherapy according to the protocol of the hospital. Treatment responses were assessed at the end of 4 weeks. The prognostic indicators were used in a Poisson model for multiple regression analysis to estimate the relative risk of the main prognostic variables.

Main Outcome Measures: Response of the ulcer to treatment.

Results: Of the 115 patients analyzed in the study, 52 (45.2%) were treatment successes, 27 (23.5%) had slow-healing ulcers, and 36 (31.3%) were refractory to primary treatment. Multivariate analysis showed that the predictors of treatment failure were ulcers that exceeded 14 mm² ($P = 0.009$), the presence of hypopyon ($P = 0.003$), and identification of *Aspergillus* ($P = 0.003$).

Conclusion: In patients with fungal keratitis treated with 5% natamycin monotherapy, larger ulcer size and infection with *Aspergillus* were predictors of a poor outcome. *Ophthalmology* 2006;113:526–530 © 2006 by the American Academy of Ophthalmology.

Corneal scarring due to trauma or infections is a major cause of monocular blindness, especially in developing countries.^{1–3} A previous study reported that the incidence of corneal infections in India is almost 10 times that reported in the United States.⁴ This is likely to be the case in other developing countries as well. In addition to an increased incidence, there is also a greater diversity of causative organisms in these areas. Fungi have replaced bacteria as the predominant cause of infectious keratitis in some of these countries.^{5,6}

Visual outcomes after fungal keratitis are often unsatisfactory; one study reported a 25% evisceration rate in eyes with this infection.⁶ Although risk factors for this condition (i.e., trauma, contact lens use, topical steroid use, and other ocular surface disorders⁷) have been recognized, little is known about how these and other risk factors may affect the

outcome of an infection. The purpose of this prospective study was to identify risk factors predictive of impaired healing of the ulcers.

Materials and Methods

This prospective, nonrandomized, interventional, comparative study was performed at the Cornea Department of Aravind Eye Hospital, Madurai, India, after approval by the institutional review board of the Aravind Medical Research Foundation. Each patient with keratitis underwent a detailed clinical examination using a slit-lamp biomicroscope to measure the size and depth of the ulceration, after the recording of a detailed clinical and demographic history that included duration of the symptoms, details about past and concurrent ocular diseases, circumstances under which the eye became infected, history of trauma, contact lens use, and use of any ocular medications. Visual acuity was measured in logarithm of the minimum angle of resolution units.

The corneal ulcer was scraped using a Kimura spatula under magnification, and the material obtained was subjected to Gram's staining and 10% potassium hydroxide mounts. Subsequent scrapings were plated onto blood agar and potato dextrose agar. Patients with an ulceration of at least 2 mm² and a smear positive for fungus were potential participants. Those who were unwilling to participate, those with total or perforated corneal ulcers, and those who had mixed infections were excluded from the study.

After informed consent was obtained, subjects were treated according to the protocol of the department. The patients were instructed to instill 5% natamycin eye drops (Sun Pharmaceuticals, Mumbai, India) on an hourly basis between 7 AM and 9 PM; 1% atropine sulfate ointment also was prescribed for use twice daily at

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Table 1. Treatment Success, Primary Treatment Failure, and Slow Healing in Subgroups of Patients with Fungal Keratitis

Characteristics at Diagnosis	N	Treatment Success (Group 1)		Slow Healing (Group 2)		Primary Treatment Failure (Group 3)	
		n = 52	%	n = 27	%	n = 36	%
Age (yrs)							
≤40	58	30	51.72	19	32.76	9	15.52
>40	57	22	38.60	8	14.04	27	47.37
Gender							
Male	64	23	44.23	21	77.78	20	55.56
Female	51	29	55.77	6	22.22	16	44.44
Duration of symptoms (days)							
≤7	69	37	71.15	14	51.85	18	50.00
>7	46	15	28.85	13	48.15	18	50.00
Trauma							
Present	78	48	92.31	14	51.85	16	44.44
Absent	37	4	7.69	13	48.15	20	55.56
Concurrent factors							
Present	17	1	1.92	14	51.85	2	5.56
Absent	98	51	98.08	13	48.15	34	94.44
Recent corticosteroids							
Present	6	3	5.77	0	0.00	3	8.33
Absent	82	34	65.38	24	88.89	24	66.67
Recent native medicine							
Present	20	8	15.38	6	22.22	6	16.67
Absent	68	29	55.77	18	66.67	21	58.33
Recent antiinfective agents							
Present	63	26	50	18	66.66	19	54.29
Absent	52	26	50	9	33.34	17	45.71
Ulcer size (mm ²)							
≤14	69	44	84.62	15	55.56	10	30.56
>14	46	8	15.38	12	44.44	26	69.44
Depth of infiltrate							
Deep	31	4	7.69	7	25.93	20	55.56
Middle	39	17	32.69	11	40.74	11	30.56
Superficial	41	30	57.69	8	29.63	3	8.33
Hypopyon (≥2 mm)							
Present	19	3	5.77	0	0.00	16	44.44
Absent	96	49	94.23	27	100.00	20	55.56
Culture result							
Positive	80	29	55.77	21	77.78	30	83.33
Negative	35	23	44.23	6	22.22	6	16.67
Fungal genus							
<i>Aspergillus</i>	28	4	7.69	6	22.22	18	50.00
<i>Fusarium</i>	28	12	23.08	10	37.04	6	16.67
Other filamentous fungi	24	13	25.00	4	14.81	6	16.00
Current treatment							
Natamycin	89	50	96.15	19	70.37	22	61.11
Ketoconazole	3	0	0.0	2	7.4	1	2.78
Both	19	2	3.85	6	22.22	11	30.56

least 15 minutes after the application of the natamycin eyedrops. Very large ulcers (>50 mm²) also were treated with systemic ketoconazole (400 mg/day). The patients were examined again at weekly intervals or more often if the clinical situation warranted. Each subject was examined at the slit lamp, and the size and depth of the infiltrate were recorded for up to 4 weeks after entry into the study. The presence or absence of hypopyon in the anterior chamber was noted and quantified in millimeters. An ulcer was considered healed if the epithelial defect had healed with no staining on fluorescein application and no progression of the stromal infiltration (group 1). An ulcer was considered to have delayed healing if the size of the ulcer decreased by at least 20% but had not fully healed and still required treatment (group 2). An ulcer was considered to have failed treatment if the size remained the same or increased or if the ulcer perforated and required surgical intervention (group 3).

Potential prognostic factors were compared among the 3 groups and included mean patient age, gender, history of trauma, size of the ulcer at presentation, depth of the ulcer, concurrent morbidity, culture results, and treatment history. An initial univariate and stratified analysis was performed to identify and select important risk factors for subsequent inclusion in the regression model. Multiple regression analysis using Poisson models was used to estimate the relative risk of the main prognostic factors. $P < 0.05$ was considered statistically significant.

Results

We recruited 140 eyes of 140 patients with fungal keratitis who presented to the cornea clinic from April to September 2004. Because 25 patients (18%) were lost to follow-up, the results

Table 2. Significant Predictors for Primary Treatment Failure in Fungal Keratitis

Characteristic	No. of Patients (%)	Risk Ratio	95% CI	P Value
Age (yrs)				
>40	27/57 (47.37)	3.05	1.58–5.91	0.0002
≤40	9/58 (15.52)			
Size of ulcer (mm ²)				
>14	26/46 (56.52)	3.90	2.08–7.29	<0.0001
≤14	10/59 (14.49)			
Trauma				
Present	16/78 (20.51)	0.38	0.22–0.65	0.0003
Absent	20/37 (54.05)			
Hypopyon (≥2 mm)				
Present	16/19 (84.21)	4.04	2.61–6.25	<0.0001
Absent	20/96 (20.83)			
Culture result				
Positive	30/80 (37.5)	2.18	1.001–4.77	0.03
Negative	6/35 (17.14)			
Deep infiltrate				
Present	16/24 (64.52)	3.68	2.14–6.34	<0.0001
Absent	12/65 (17.50)			
Fungal genus				
<i>Aspergillus</i>	18/28 (64.29)	2.92	1.62–5.27	<0.0001
Others	11/50 (22.00)			
Multiple Adjusted Poisson Regression				
Variables in Regression Model		Adjusted Risk Ratio	95% CI	P Value
Size of ulcer (>14 mm ² vs. ≤14 mm ²)		2.80	1.33–5.93	0.009
Hypopyon		3.20	1.64–6.27	<0.003
<i>Aspergillus</i>		3.05	1.57–5.93	0.003

CI = confidence interval.

presented are from 115 (82%) patients. No patients were debilitated or immunocompromised or had diabetes or human immunodeficiency virus. No patients had a history of contact lens use.

The mean age of the patients was 41.8 years (range, 5–75), and 64 (55.6%) were males. Mean time from the onset of pain to presentation at the hospital was 9.6 days (standard deviation, 7.88; range, 2–42).

Table 3. Significant Predictors for Perforation in Fungal Keratitis

Characteristic	No. of Patients (%)	Risk Ratio	95% CI	P Value
Age (yrs)				
>50	10/24 (41.67)	2.67	1.32–5.40	<0.01
≤50	12/77 (15.58)			
Ulcer size (mm ²)				
>14	15/35 (42.86)	4.04	1.82–8.97	<0.01
≤14	7/66 (10.61)			
Hypopyon				
Present	8/11 (72.73)	4.67	2.56–8.54	<0.0001
Absent	14/90 (15.56)			
Deep infiltrate				
Present	12/23 (52.17)	4.06	2.02–8.18	<0.0001
Absent	10/78 (12.82)			
Fungal genus				
<i>Aspergillus</i>	13/23 (56.52)	4.90	2.41–9.98	<0.01
Others	9/78 (11.54)			
Multiple Adjusted Poisson Regression				
Variables in Regression Model		Adjusted Risk Ratio	95% Confidence Limits	P Value
Hypopyon		3.38	1.39–8.26	<0.01
Deep infiltrate		2.78	1.17–6.57	0.01
<i>Aspergillus</i>		4.53	1.93–10.60	<0.01

CI = confidence interval.

Table 4. Correlation among the 3 Variables with the 3 Groups of Fungi

Fungal Genus	Mean Size of Ulcer (mm ²)	Hypopyon (> 2 mm) Present	Deep Infiltrate Present
<i>Aspergillus</i>	18	2 (16%)	8 (38%)
<i>Fusarium</i>	17	6 (50%)	9 (42%)
Other filamentous fungi	12	4 (33%)	4 (19%)
P value	0.131	0.0232	0.828

Table 1 shows the baseline clinical characteristic of the 3 patient groups. The mean size of the ulcer was 14 mm². A positive fungal culture was obtained in 80 patients (70%). *Fusarium* (n = 28/80) and *Aspergillus* (n = 28/80) were the most common isolates and together accounted for 70% of the culture-positive organisms. The other organisms isolated were *Curvularia*, *Scedosporium*, and *Botryodiplodia*. None of the ulcers was infected with *Candida*.

Based on our study definition, 52 patients (45.2%) were classified in group 1, 27 patients (23.5%) were classified in group 2, and 36 patients (31.3%) were classified in group 3.

Rates of positive cultures were 55.77% in group 1, 77.78% in group 2, and 83.33% in group 3.

Multivariate analysis identified an ulcer greater than 14 mm² (95% confidence interval [CI], 1.33–5.93; *P* = 0.009), presence of hypopyon (95% CI, 1.42–5.57; *P* = 0.003), and growth of *Aspergillus* (95% CI, 1.39–5.32; *P* = 0.003) as the most significant risk factors for primary treatment failure (group 3) (Table 2). Twenty-two (61%) of the group 3 patients developed perforation. Deep ulcers that cultured positive for *Aspergillus* (*P* < 0.01) and an associated hypopyon of more than 2 mm (*P* < 0.01) were more likely to perforate (Table 3). Even though there was no difference regarding ulcer size, ulcer depth, and presence of hypopyon among the ulcers caused by different genera of fungi, those caused by *Aspergillus* were refractory to primary treatment (Table 4).

Discussion

Despite the known potential for visual impairment and blindness associated with fungal keratitis, few research studies have evaluated the risk factors and treatment outcomes.

In the current study, the rate of primary treatment failure was 31%. This number is significantly higher than those reported with bacterial keratitis.^{8,9} This factor also has been corroborated by Wong et al,¹⁰ who concluded that fungal ulcers were more likely to perforate, thus requiring keratoplasty more often.

Fusarium and *Aspergillus* are the most common causes of fungal keratitis in the developing world.⁴ Natamycin is the most effective medication against these organisms.^{11,12} In a previous study, natamycin and econazole were equally effective against *Aspergillus* and *Fusarium*.¹³ In addition, concurrent use of 5% natamycin and 2% econazole did not seem to offer additional benefits over monotherapy with 5% natamycin in the management of fungal keratitis.¹⁴ Based on these studies and according to our clinical protocol, natamycin was administered as monotherapy in 94% of the patients in the current study, and in the remaining 6%, oral ketoconazole was added.

As expected, poor healing was associated with larger and deeper ulcers. In addition, ulcers caused by *Aspergillus* were most likely to be refractory to treatment. In his classic article on the principles in the management of oculomycosis, Jones¹⁵ reported that *Fusarium solani* was far more destructive than *Aspergillus* and many other fungal species. However, our data suggested otherwise. When treated with topical 5% natamycin monotherapy, ulcers caused by *Aspergillus* were more likely to be refractory to treatment than those caused by *Fusarium*. This also highlights the need for a detailed microbiology workup, including culture, in areas in which infectious keratitis is more prevalent. Antifungal drug sensitivity tests need to be developed and standardized to select appropriate antifungal agents depending on the organism isolated.

Modifications of existing therapeutic regimens for fungal keratitis are not tried frequently, due to the paucity of available antifungal agents and their prohibitive costs. In a clinical series, Jones et al¹² reported that multiple concurrent antifungal medications might be needed 5% of the time. In our study, neither alternative topical agents other than natamycin nor subconjunctival and systemic antifungals were used routinely, and the possible beneficial effect of these agents could not be assessed. Larger ulcers caused by *Aspergillus* may have to be managed with alternative topical antifungals, additional systemic antifungals, or both to prevent treatment failure.

The increased incidence of fungal keratitis, coupled with a decreased availability of donor corneas in developing countries, warrants further study of the risk factors, antifungal susceptibility testing, and possible pharmacologic combinations to prevent blindness.

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