

**C**ONTINUING  
**P**ROFESSIONAL  
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**ARTICLE**

# REVIEW OF FUNGAL KERATITIS

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## INTRODUCTION

The outbreak of infectious fungal keratitis last year received timely and comprehensive attention from all cadres of eye care personnel involved. Given the extent of the problem, many clinical questions have surfaced in response to the detection and management of this particularly rare cause of keratitis. Fungal keratitis, if not diagnosed and treated with celerity, can be rapidly destructive to the integrity of the eye, resulting in devastating ocular damage. Unfortunately, delayed diagnosis is common, primarily because of the lack of suspicion, and even if the diagnosis is made accurately, management remains a challenge. Poor corneal penetration and limited commercial availability of antifungal drugs further exacerbate the management quagmire.

## BACKGROUND

Fungal keratitis was first described by Leber in 1879. Whilst this entity is not a common cause of corneal infection, it certainly represents one of the major causes of infectious keratitis in tropical areas of the world. The incidence of fungal keratitis has increased over the past 30 years as a result of the frequent use of ocular corticosteroids; a rise in the number of patients who are immuno-compromised, and the availability of laboratory diagnostic techniques that aid in its diagnosis.<sup>1</sup>

## AETIOLOGY

The incidence of fungal keratitis varies according to geographical location. *Aspergillus* is the most common cause of fungal keratitis worldwide (27-64%), followed by *Fusarium* (6-32%) and *Penicillium* (2-29%) species.<sup>1</sup>

## GENDER PREDILECTION

Fungal keratitis is more common in males than in females and often occurs in patients with a history of outdoor ocular trauma.<sup>2</sup>

## RISK FACTORS

- Previous history of ocular trauma (especially if organic matter is involved)
- Agricultural occupations
- Age
- Pre-existing ocular disease
- Exposure keratopathy
- Chronic keratitis
- Chronic use of steroids
- Systemic Immunosuppressive disease

Corneal trauma is the most frequent and major risk factor for fungal keratitis. There should be a high level of suspicion if a patient presents with a history of corneal trauma, particularly with plant or soil matter. The trauma that accompanies contact lens wear is miniscule. Contact lenses are not a common risk factor of fungal keratitis. *Candida* is the principal cause of keratitis associated with therapeutic

contact lenses wear and filamentous fungi are the ones associated with refractive contact lens wear.<sup>2</sup>

## PATHOPHYSIOLOGY

Several different fungi have been implicated as causing fungal keratitis. However, the two medically important groups responsible of corneal infection are yeast, and filamentous fungi. Many fungal organisms associated with ocular infections are ubiquitous, saprophytic organisms and have been reported as causes of infection only in the ophthalmic literature.<sup>2</sup>

### *Yeast Fungi*

*Candida* (an opportunistic yeast that is part of the normal human flora) ulcers commonly occur in eyes with predisposing alterations in the host defenses, including chronic use of corticosteroids, exposure keratitis, keratitis sicca, herpes simplex keratitis and prior keratoplasty. *Candida* ulcers occasionally have oval outlines with a plaque like surface, or can produce a relatively indolent stromal infiltration with smaller satellite lesions.

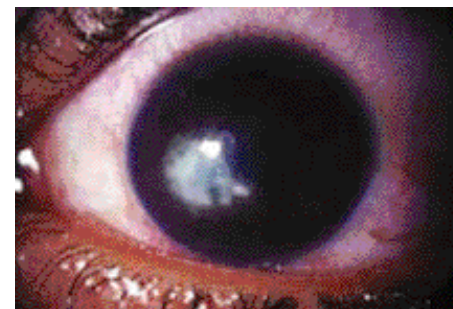
### *Filamentous Fungi*

*Fusarium*, *Cephalosporium* and *Aspergillus* are the most common types of filamentous fungi found. These organisms usually infect normal eyes following mild abrasive corneal trauma, especially after injury from vegetable matter. Filamentous fungi may have a grey or dirty-white dry, rough, textured surface with an elevated margin. There may be feathery extensions beneath the epithelium into the adjacent stroma. Satellite lesions separated from the central infectious area may occur and correspond to microabscesses in the surrounding tissue.

## PRESENTING SYMPTOMS OF THE PATIENT

### SYMPTOMS

- Pain which is severe at first, but may diminish as corneal nerves are damaged
- Foreign body sensation
- Increased eye pain or discomfort
- Decrease in vision
- Hypersensitivity to light
- Blepharospasm
- Epiphora



Picture 1 - Fungal Keratitis 1

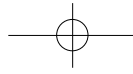
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## CLINICAL PRESENTATION

The clinical appearance of fungal keratitis varies greatly depending on the duration and severity of infection.

### Non Specific signs

- Conjunctival injection
- Epithelial defect
- Suppuration
- Stromal Infiltration
- Anterior chamber reaction
- Hypopyon
- Aqueous Flare
- Corneal Neovascularisation

### Specific Signs

- Infiltrates with feathery margins, rough texture, raised borders, brown pigmentation, associated endothelial plaque, and satellite lesions
- Deep stromal infiltrates with an intact epithelium
- Dull grey appearance of the cornea with possible heaping of epithelium

Sclerotic scatter can be used to highlight the density and scalloped borders of the fungal lesion. Many fungal ulcers demonstrate no striking morphological pattern, and it often is not possible to differentiate clinically between fungal keratitis and bacterial keratitis.

## DIAGNOSIS

A diagnosis of fungal keratitis is based on a matrix of the following:

1. Case history
2. Clinical signs
3. Confirmation from cytology and/or culture results.<sup>2</sup>

## LABORATORY TESTS

The most important step in the initial management of suspected fungal keratitis is to obtain corneal material for direct smears and inoculation of media. Smears are used to obtain information about the pathogen. Gram stain may identify the yeast forms of *Candida*, and Giemsa stain is more likely to detect filamentous fungus. It is important to scrape multiple sites in the ulcer crater, particularly at the margins, to enhance recovery of the organisms. If fluorescein microscopy is available, acridine orange and calcofluor white are the stains of choice. The primary isolation cultures for fungus are Sabouraud and blood agar at room temperature.

## ANTIFUNGAL THERAPY

Antifungal therapy should be limited to cases with positive fungal smears or cultures. Current available antifungal medications belong to the groups of polyenes, pyrimidines, imidazoles and triazoles. (Summarized in Table 1)

Although, polyenes penetrate ocular tissue poorly, **Amphotericin B** is the drug of choice for yeast infections. In addition, it has efficacy against many filamentous fungi. Administration is every 30 minutes for the first 24 hours and every hour for the second 24 hours. Thereafter, it can be very slowly tapered according to the clinical response. **Natamycin** is the only commercially available topical ophthalmic antifungal preparation. It is effective against filamentous fungi, particularly for infections caused by *Fusarium*. However, due to poor ocular penetration it has only been useful in cases with superficial corneal infection.<sup>2</sup>

**Fluocytosine** may be given with **Amphotericin B** or **Miconazole**. It is synergistic with these medications. Otherwise, if this is the only drug used in therapy for *Candida* infections, emergence of resistance rapidly develops. Fluocytosine should therefore never be used alone.

Imidazoles and triazoles are synthetic chemical antifungal agents. High corneal levels of ketoconazole and fluconazole have been demonstrated in animal studies. Due to the excellent penetration into ocular tissue, these medications are given systemically. Ketoconazole dose for adults is 200-400mg/day, which can be increased to 800 mg. However, because of the secondary effects, careful increasing of the dose should be done. The promotion of fungal growth by corticosteroid treatment is well recognized. Therefore, corticosteroids must be avoided in the early of therapy fungal keratitis. If there is evidence that an effective antifungal agent is being used and that clinical infection is well under control, corticosteroids can be used cautiously late in the treatment to reduce stromal or anterior segment inflammation.

Successful antifungal therapy requires frequent drug administration for prolonged periods. The minimal requirement for most cases especially where the posterior part of the stroma is affected is 12 weeks. The cornea must be monitored for toxicity. Some corneal manifestations of toxicity are:

1. Protracted epithelial ulceration
2. Punctuate corneal epithelial erosion
3. Diffuse stromal haze

Organism	First choice	Second choice
Yeast	• Fluocytosine, 1% drops*	Miconazole 1% drops*
Filamentous	Amphotericin B, 0.15%	Clotrimazole, 1% cream
Superficial	drops*	Fluconazole, 200mg
Deep	• Fluocytosine, 150 mg/kg p.o	p.o
	Natamycin, 5% Suspension	Amphotericin B, 0.15mg Drops*
	Amphotericin B, 0.15% Drops	Miconazole, 1%drops*
	Rifampin	Ketoconazole, 400mg p.o

Table two - Current antifungal treatment (\*All drops administered hourly around the clock)<sup>1</sup>

## SURGICAL THERAPY

Surgical therapy may be required not only for complications of acute infectious processes, but also because should medical management fail.

### Debridment

Debridement is the simplest form of surgical intervention. The organisms and necrotizing material is removed and the penetration of antifungal medications is enhanced by the removal of the epithelium, which is a barrier for the topical antifungals. Debridement should be performed every 24 to 48 hours.

### Biopsy

A biopsy is indicated for the direction of diagnostic and/or therapeutic treatment.

### Conjunctival Flaps

Conjunctival flaps have been advocated for nonhealing ulcers and are often effective, although fungal organisms have been found to persist under a conjunctival flap.

### Penetrating keratoplasty (PK)

Penetrating keratoplasty should be performed sooner rather than later in cases not responding to aggressive antifungal therapy. If the infectious process progresses and the fungus reaches the limbus or sclera, it will be too late for keratoplasty to rid the eye of viable fungus, and the eye will be destroyed by the fungal infection.

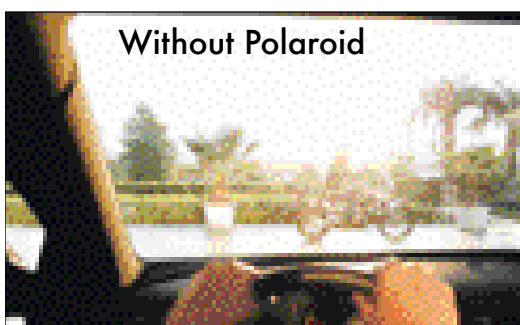
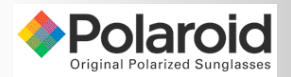
### Lamellar keratoplasty

Lamellar keratoplasty may be ineffective in treating fungal keratitis

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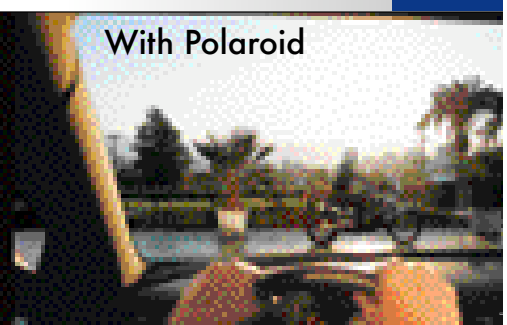
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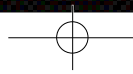
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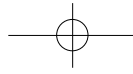
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because of the inability to remove the infectious agent. If the area of infection can be completely encompassed by the penetrating graft, and if there has been an inadequate response to medical treatment, the corneal graft may be an effective cure.

## PATIENT MANAGEMENT

Typically, diagnosis occurs late, as many practitioners frequently misdiagnose fungal keratitis as bacterial keratitis. Fungal keratitis is considered only after a presumed bacterial keratitis worsens during antibiotic therapy.

Fungal keratitis is difficult to treat for various reasons. Few antifungal medications have good corneal penetration, and most are merely fungistatic hence requiring an intact immune system and a prolonged therapeutic course. Except for natamycin 5%, all antifungal medications must be adapted for ophthalmic use from systemic drugs. The result is considerable ophthalmic toxicity.

The three major goals for treating fungal keratitis are:

1. Eradicate the fungal infection
2. Prevent secondary bacterial infection
3. Control ocular pain

Analgesic therapy includes cycloplegics and nonsteroidal anti-inflammatory drugs. Atropine 1% ophthalmic solution or ointment should be applied topically, as frequently as is necessary, to maintain pupillary dilation. It not only blocks painful ciliary spasm but also minimizes the development of synechiae. Ocular pain may also be controlled by the systemic administration of non-steroidal anti-inflammatory drugs. Secondary glaucoma may require oral carbonic anhydrase inhibitors or hyperosmotic agents. Additional antibacterial therapy for individual cases should be guided by culture and sensitivity testing results. Because secondary bacterial invasion is likely, topical antibiotics should be included in the therapeutic regimen. Initial antibacterial therapy should be directed against both gram-positive and gram-negative organisms.<sup>3</sup>

Medical treatment can be effective, provided that suitable drugs are administered appropriately. Combinations of surgical and medical treatment usually reduce the duration of therapy, although surgical treatment can produce more scarring. Surgery is often chosen because of the shorter recovery time and potential better prognosis.

Decisions about alternate therapy must be based on the biomicroscopic signs and tolerance of the topical medications.

Improvement in clinical signs may be difficult to detect during the initial several days of effective antifungal therapy. However some of the biomicroscopic signs that may be helpful to evaluate efficacy are:

1. Blunting of the perimeters of the infiltrate
2. Reduction of the density of the suppuration
3. Reduction in cellular infiltrate and edema in the surrounding stroma
4. Reduction in A/C inflammation
5. Progressive re-epithelization
6. Loss of the feathery perimeter of the stromal inflammation

If the smear and cultures are negative at 48 to 72 hr in a patient with strong suspicion of having fungal infection, and the patient is not improving on the initial, broad-spectrum antibacterial therapy chosen, a corneal biopsy is required. If the corneal biopsy is still negative, the destructive corneal process is progressing, and hypopyon exists; anterior chamber paracentesis or excisional biopsy (keratoplasty) should be performed.

## CONCLUSION

Despite not being able to treat the patient with fungal keratitis, it is imperative that the optometrist be able to identify signs of fungal keratitis by means of a thorough case history and a detailed slit lamp biomicroscopy exam. As the possible first line of medical interaction with the patient, the optometrist needs to be circumspect and direct the patient to appropriate treatment. The optometrist also need to be in a position of knowledge that he/she may be able to answer any questions that the patient may have about this potentially devastating ocular condition.

## REFERENCES

1. Handbook of Ocular Disease Management. (<http://revoptom.com>)
2. Pavan-Langston, D, 2002 Manual of Ocular Diagnosis and Therapy, Lippincott William & Wilkins, Massachusetts.
3. Edsel I *et al.* (2005) Fungal Keratitis (<http://emedicine.com>)
4. Kanski, JJ, 1999 Clinical Ophthalmology, Butterworth-Heinemann, Woburn

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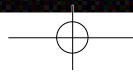
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**Multiple choice: select the most appropriate correct answer and mark your responses on the attached form.**

1. Fungal keratitis represents one of the major causes of infectious keratitis in developing countries.
  - a. True
  - b. False
2. Fusarium is the most common cause of fungal keratitis worldwide
  - a. True
  - b. False
3. Risk factors for fungal keratitis exclude:
  - a. Age
  - b. Exposure keratopathy
  - c. Chronic keratitis
  - d. Race
4. Candida is the principal cause of keratitis associated with refractive contact lenses wear and filamentous fungi are the ones associated with cosmetic contact lens wear.
  - a. True
  - b. False
5. Candida ulcers occasionally have oval outlines with a plaque like surface.
  - a. True
  - b. False
6. Symptoms of fungal keratitis include:
  - a. Ocular pain
  - b. Improved contrast sensitivity
  - c. Blepharospasm
  - d. Excessive Tearing
7. Clinical presentation depends primarily on the type of fungal infection
  - a. True
  - b. False
8. Slit lamp Biomicroscopy can reveal the following signs in a patient with fungal keratitis:
  - a. Limbitis
  - b. Fixed dilated pupil
  - c. Lenticular changes
  - d. Hyperemia
9. The differential diagnosis for fungal keratitis is:
  - a. Vernal Conjunctivitis
  - b. Acute anterior uveitis
  - c. Bacterial Conjunctivitis
  - d. Adenoviral 13 Conjunctivitis
10. Diagnosis of fungal keratitis is based on cytology finding exclusively
  - a. True
  - b. False
11. Gram stain is used to identify the yeast forms of Candida, and Giemsa stain is used to detect filamentous fungus
  - a. True
  - b. False
12. Amphotericin B is the only commercially available topical ophthalmic antifungal preparation.
  - a. True
  - b. False
13. \_\_\_\_\_ is the drug of choice for yeast infections.
  - a. Natamycin
  - b. Amphotericin B
  - c. Miconazole
  - d. Flucytosine
14. \_\_\_\_\_ is a synthetic chemical antifungal agents
  - a. Miconazole
  - b. Amphotericin B
  - c. Natamycin
  - d. Flucytosine
15. Corticosteroid therapy if strictly forbidden in a patient with fungal keratitis
  - a. True
  - b. False
16. Post recovery from fungal keratitis is \_\_\_\_\_ weeks
  - a. 1 week
  - b. 3 weeks
  - c. 6 weeks
  - d. 12 weeks
17. \_\_\_\_\_ is simplest form of surgical intervention.
  - a. Corneal Biopsy
  - b. Conjunctival Flap
  - c. Debridement
  - d. Anterior Chamber Paracentesis
18. Pain relievers for the patient with fungal keratitis can be
  - a. Oral carbonic anhydrase inhibitors
  - b. Beta Blockers
  - c. Cycloplegic agents
  - d. Topical Antibiotics
19. Biomicroscopic signs of improvement include:
  - a. Pointing of the perimeters of the infiltrate
  - b. Increase of the density of the suppuration
  - c. Increase in cellular infiltrate and edema in the surrounding stroma
  - d. Reduction in A/C inflammation
20. The major goal for treating fungal keratitis is:
  - a. Delay secondary bacterial infection
  - b. Eradicate the fungal infection
  - c. Prevent synechiae formation
  - d. Decrease IOP



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## REVIEW OF FUNGAL KERATITIS

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