# EPIDEMIOLOGY, DIAGNOSIS AND MANAGEMENT OF FUNGAL KERATITIS

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Microbial keratitis continues to be a leading cause of ocular morbidity and blindness worldwide.[1] Fungal keratitis accounts for 30 to 50% of all cases of microbial keratitis in developing countries.[1-4] In recent times there has been an increase in awareness and recognition of the clinical signs of fungal keratitis, particularly in geographic areas where these infections are common; such as tropical and subtropical parts of the world. Increased awareness coupled with improved laboratory and *in vivo* diagnostic techniques have led to an increase in the frequency of correct diagnosis and consequent increase in prevalence of the disease.

**Epidemiology**

The epidemiological features of fungal keratitis vary among different geographic regions and climate conditions.[5] It occurs more frequently in warm and dry climate than in temperate zones. It may vary considerably between countries and also within countries. It is essential to determine local etiology within a given region when planning a corneal ulcer management strategy. Several studies have investigated the epidemiology of corneal ulceration and causative microorganisms. *Fusarium spp.* and *Aspergillus spp.* are the most common fungi isolated from patients of the tropics, while *Candida albicans* is the most common pathogen of mycotic keratitis in temperate region.

**Risk Factors**

Fungi are a normal part of the microbial environment. Although the eye is continuously exposed to these microorganisms, the normal external ocular defences including the eyelids and tear components, provide adequate protection. Fungal infections, in the absence of a predisposing factor (Table-1), are unusual in human cornea.

The importance of trauma, often trivial and frequently associated with plant material, is well documented in the initiation of fungal infection. Fungi may be responsible for some cases of microbial keratitis associated with contact lens wear. It can grow within matrix of the contact lenses. Wearing contact lens may be categorized as a major cause of minor injuries where either microbes present in the atmosphere or the contaminated lens preservation solution is generally responsible for the onset of corneal ulcers. Fungal keratitis has been reported from cosmetic (phakic and aphakic) contact lens wearer and therapeutic lens user.

Prolonged use of topical broad-spectrum antibiotics and indiscriminate use of steroids has been described to be associated with fungal keratitis. This may be attributed to disturbance in the microbial flora of the eye and local immunosuppression.

Other less common risk factors include vernal or allergic keratoconjunctivitis, ocular surface disorder, penetrating keratoplasty, bullous keratopathy and exposure keratitis. Recently several reports of fungal keratitis after laser refractive surgery have also been published.[27,28]

**Clinical Features**

The onset of fungal infection of cornea is mostly insidious although it may not present as acutely as bacterial keratitis. Classical clinical features of fungal keratitis may vary considerably. A prospective study looking at the characteristic clinical features as an aid to the diagnosis concluded that no one clinical feature can be considered as absolutely pathognomonic of a particular type of etiological agent.[29]

The traditional academic approach for the initial diagnosis and management of microbial keratitis, considers diagnostic scraping of corneal ulcers mandatory. However, this requires a well-equipped laboratory with trained manpower

Table-1: Mycotic keratitis - a review of the literature

| Place | Year | Cases | %Fungi | Organism-1 | Organism-2 | Risk factor |
|---|---|---|---|---|---|---|
| **Europe** | | | | | | |
| France[6] | 2002 | 19 | ---- | *Candida spp.*, 58% | *Aspergillus spp.*, 21%<br>*Fusarium spp.*, 21% | Topical steroid treatment (42.1%), corneal graft (31.6%), trauma or foreign body (31.6%). |
| London[7] | 2007 | 66 | ---- | *Candida spp.*, 60.6% | *Fusarium spp.*, 18.18% | Ocular surface disease or a prior penetrating keratoplasty (97.4%) for *Candida spp.* Trauma (30.8%) or cosmetic contact lens wear (30.8%) for filamentary fungal infection. |
| **North America** | | | | | | |
| Florida[8] | 1994 | 125 | ---- | *Fusarium spp.*, 62% | *Candida spp.*, 12.5% | Trauma (44%). five patients were using extended wear contact lenses and one patient was wearing a therapeutic bandage contact lens. |
| Philadelphia[9] | 2000 | 24 | ---- | *Candida albicans*, 46% | *Fusarium spp.*, 25% | Chronic ocular surface disease (41.7%), contact lens wear (29.2%), atopic disease (16.7%), topical steroid use (16.7%), and ocular trauma (8.3%). |
| New York[10] | 2006 | 5083 | 1.2% | *Candida spp.*, 48% | *Fusarium solani*, 10% | Human immunodeficiency virus (HIV) seropositivity (15 eyes), chronic ocular surface disease (14 eyes), and trauma (7 eyes). |
| **South America** | | | | | | |
| Paraguay[11] | 1991 | 26 | 58% | *Fusarium spp.*, 42% | *Aspergillus spp.*,19% | ---- |
| **Africa** | | | | | | |
| Ghana (Accra)[4] | 1995 | 199 | 34% | *Fusarium spp.*, 52% | *Aspergillus spp.*, 15% | ---- |
| Tanzania[12] | 1999 | 212 | 15% | *Fusarium spp.*, 75% | *Aspergillus spp.*, 19% | Human immunodeficiency virus (HIV) seropositivity (81.2%) |
| **Australia & New Zealand** | | | | | | |
| New Zealand[13] | 2003 | 103 | 4% | ---- | ---- | ---- |
| Australia[14] | 2007 | 56 | ---- | *Candida albicans*, 37.2% | *Aspergillus fumigatus*, 17.1% | Ocular trauma (37.1%), chronic steroid use (31.4%) and poor ocular surface (25.7%) |
| **Asia** | | | | | | |
| Bangladesh[15] | 1991 | 127 | 34% | *Aspergillus spp.*, 49% | *Fusarium spp.*, 28% | ---- |
| Nepal, Kathmandu[16] | 1991 | 405 | 17% | *Aspergillus spp.*, 47% | *Candida spp.*, 13% | ---- |
| Saudi Arabia[17] | 1992 | 191 | 14% | *Aspergillus spp.*, 41% | *Fusarium spp.*<br>*Candida albicans* | ---- |
| Bangladesh[3] | 1994 | 66 | 36% | *Aspergillus spp.*, 40% | *Fusarium spp.*, 21% | Injury due to rice grains. |
| Sri Lanka[18] | 1994 | 66 | 33% | *Aspergillus spp.*, 18% | single isolates | ---- |
| Thailand[19] | 1995 | 145 | 25% | *Aspergillus spp.*, 34% | *Fusarium spp.*, 26% | ---- |

Table-1 (contd..)

| Place | Year | Cases | %Fungi | Organism-1 | Organism-2 | Risk factor |
|---|---|---|---|---|---|---|
| India, New Delhi[20] | 1997 | 211 | 10.8% | *Aspergillus spp*., 40% | *Fusarium spp*., 11% | Trauma (55.3%), associated systemic illness (11.2%), previous ocular surgery (9.8%). Corneal injury contaminated with vegetable matter was responsible for 60.5% of traumatic cases. |
| India, Madurai[1] | 1997 | 434 | 35% | *Fusarium spp*., 47% | *Aspergillus spp*., 16% | ---- |
| Singapore[21] | 1997 | 29 | ---- | *Fusarium spp*., 52% | *Aspergillus flavus*, 17% | Ocular trauma (>50%), antecedent topical corticosteroid therapy (25%). |
| Bangladesh[22] | 1998 | 63 | ---- | *Aspergillus spp*., 35%<br>*Fusarium spp*., 35% | | ---- |
| India, Mumbai[23] | 1999 | 367 | ---- | *Aspergillus spp*., 60% | *Candida spp*., 10% | Antecedent corneal trauma (89.92%) |
| Hong Kong[24] | 2001 | 223 | 2% | *Fusarium spp*., 60% | | ---- |
| India, Hyderabad[2] | 2002 | 3399 | 39.8% | *Fusarium spp*., 37.2% | *Aspergillus spp*., 30.7% | Ocular trauma (54.4%) |
| India, East[25] | 2005 | 1198 | 62.7% | *Aspergillus spp*., 59.8% | *Fusarium spp*., 21.2% | ---- |
| China, North[26] | 2006 | 1056 | 61.9% | *Fusarium spp*., 73.3% | *Aspergillus spp*., 12.1% | Corneal trauma (51.4%), especially injury from plants (25.7% in all patients) |

to process minute samples and involves the cost of maintaining various culture media and processing samples. Furthermore, many ophthalmologists do not have access to culture media. Therefore, it is imperative to get familiar with the classical clinical features (Figure-1).

*Classical Clinical Features*

a) Fungal keratitis classically presents as a slowly progressive disease characterized by a localized infiltrate.
b) The infiltrate is dry, white and cotton wool like, and is raised above the plane of the cornea.
c) The infiltrate has fine branching linear extensions in the surrounding cornea.
d) There may be satellite lesions and an immune ring associated with the main infiltrate.
e) Some patients may show brown to black pigmentation on the surface of the infiltrate.
f) Other features characteristics of fungal infection of cornea are: the presence of thick fluffy endothelial exudates and a thick hypopyon.

*Atypical Clinical Features*

Some of the unusual clinical signs of fungal keratitis include:

a) Presentation as dendritic keratitis mimicking Herpes Simplex epithelial keratitis.
b) Multiple mutton fat like keratic precipitates mimicking endothelitis.
c) Rapidly progressive keratitis presenting with gross thinning or perforation especially in mixed infection.
d) Ring shaped infiltrate mimicking *Acanthamoeba* keratitis.
e) Fungal infection of self-sealing wound of cataract surgery.
f) Fungal infection after laser in-situ keratomilieusis.
g) Yeast infection presenting as localized round infiltrate mimicking infection by Gram positive bacteria.
h) Infiltrate with branching linear extension mimicking *Nocardia* infection.

**Diagnosis**

A rapid and accurate diagnosis of fungal keratitis ensures specific therapy and complete recovery. A systematic approach involving elicitation of history, meticulous slit-lamp examination, confocal microscopy and appropriate microbiological methods should be employed to make a quick diagnosis.

*Non-invasive Technique*

Confocal microscopy is an imaging technique that allows optical sectioning of almost any material. It is fast emerging

as a clinically important tool in the diagnosis of various corneal conditions. It offers magnifications of up to x200 to x500 with increased image contrast and the ability to visualize details even in hazy corneas. Its non-invasive nature makes it an important modality in the rapid diagnosis of fungal keratitis. Additionally, it can be used for real time repetitive observations, which could become important in the diagnosis, management and the follow-up of cases of infective keratitis.[30]

*Invasive Technique*

**Conventional Microbiological Investigations**

Much before confocal microscopy became available; a reliable diagnosis of fungal keratitis could be made employing simple microbiological techniques. Demonstration of fungus in smears or culture of corneal scrapings remains the gold standard for diagnosis of fungal keratitis. These methods continue to be employed worldwide and require a modest laboratory set-up. Although the need to perform microbiological diagnosis is still rather controversial.[31] These investigations are essential in areas with high prevalence of fungal keratitis, which in most instances happen to be areas that may not be able to afford a confocal microscope.

**Sample Collection**

Although recommended by some we do not believe that conjunctival and lid swabs serve any purpose in the investigation of microbial keratitis, especially fungal keratitis. Samples need to be collected directly from the lesion using an instrument (such as a platinum spatula, Beaver blade, surgical blade no. 15 or blunt cataract knife) to debride material from the base and edges of the ulcerated part of the cornea. Multiple scrapings under topical anesthesia are collected and inoculated on slides and culture media as shown in Table-2. The blade or spatula may be reused if a sterile medium or sterile slide is touched but not if unsterile slides are used. It helps to keep several disposable blades available. Cotton swabs are not useful but calcium swabs have been used for recovery of fungus in culture.

Table-2: Media used for culture of bacteria, fungus, *Acanthamoeba* from corneal samples

| Type of sample | Culture media | Expected organisms |
|---|---|---|
| Corneal scrapings | • Sheep blood agar (aerobic anaerobic)<br>• Sheep blood chocolate agar<br>• Brain heart infusion broth<br>• Sabouraud dextrose agar[$]<br>• Thioglycollate broth<br>• Non-nutrient agar with *E.coli* | • Bacteria (aerobic, anaerobic)<br>• Fungi<br>• *Acanthamoeba* |
| Corneal biopsy/buttons | • Sheep blood agar (aerobic anaerobic)<br>• Sheep blood chocolate agar<br>• Brain heart infusion broth<br>• Sabouraud dextrose agar[$]<br>• Non-nutrient agar with *E.coli* | • Bacteria (aerobic, anaerobic)<br>• Fungi<br>• *Acanthamoeba* |
| Contact lenses | • Sheep blood chocolate agar (aerobic, anaerobic)<br>• Sabouraud dextrose agar[$]<br>• Non-nutrient agar with *E.coli* | • Bacteria (aerobic, anaerobic)<br>• Fungi<br>• *Acanthamoeba* |
| Contacat lens solutions | • Sheep blood chocolate agar (aerobic, anaerobic)<br>• Sabouraud dextrose agar[$]<br>• Non-nutrient agar with *E.coli* | • Bacteria<br>• Fungi<br>• *Acanthamoeba* |

[$] With antibiotics (gentamicin or chloramphenicol) but without cycloheximide. Potato dextrose agar may be used in addition to Sabouraud dextrose agar for better sporulation.

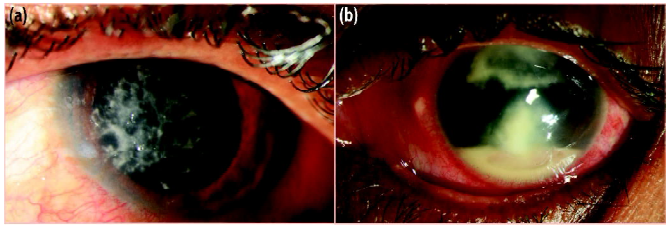


**Figure-1:** Slit-lamp photograph of fungal keratitis showing (a) hyphate edge, (b) endothelial exudate with hypopyon.

Corneal biopsy may be useful when the corneal infiltrate is situated in deeper tissues with intact epithelium. The biopsy sample should be submitted for smear, culture and histopathologic studies. Alexandrakis *et al* have demonstrated an increased recovery rate of organisms from corneal biopsy from recalcitrant culture negative cases.[32] Anterior chamber exudates have also been used for the diagnosis of fungal keratitis when endothelial exudates are present.[33]

**Direct Microscopic Examination**

Demonstration of fungal filaments or yeast in direct microscopic examination of the corneal scraping or corneal biopsy sample rapidly establishes diagnosis in a clinically presumptive case of mycotic keratitis. Several studies have documented over 85% sensitivity and specificity of fungal filament detection in a wet preparation in 10% potassium hydroxide or stained with calcofluor white or lactophenol cotton blue.

**Culture**

A culture of the corneal scraping or biopsy sample is essential to confirm diagnosis and rule out mixed infections. Clinically, there can be considerable overlap in the clinical features of bacterial, fungal and *Acanthamoeba* keratitis. A single protocol is therefore recommended for the culture of bacteria, fungi, and *Acanthamoeba* from corneal scrapings. Table-2 lists the different media that are used to culture common organisms from corneal and contact lens samples and also the incubation temperature and period required. Corneal material is inoculated on solid media in "C" streaks and liquid media are inoculated by twirling the spatula or blade in the broth. Thioglycollate broth requires the sample to be inoculated at the bottom of the tube, which can be done by transferring the material on to a cotton swab and leaving it to sink to the bottom of the tube (break off the excess length). All media except SDA or PDA (25$^{O}$C) are incubated at 37$^{O}$C. Fungal growth on culture media (Figure-2 & 3) may occur in 2-4 days although longer periods of incubation are needed (4-6 weeks) for identification.

A number of criteria have been described which help to determine the significance of fungal growth in culture. They include: presence of clinical disease suggestive of fungal infection along with either confluent growth on the inoculum in one or more solid media (Figure-4) or growth in two media or presence of fungus in direct smear examination or repeat isolation.

The conventional methods of fungal species

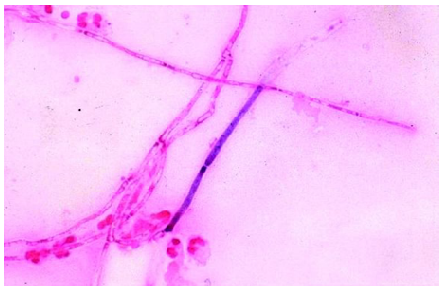

Figure-2: Gram stain of corneal scraping showing septate fungal filaments (x1000).

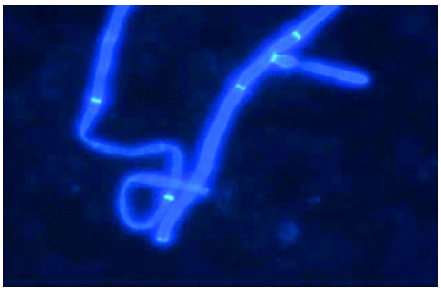

Figure-3: KOH+Calcofluor White stain of corneal scraping showing septate fungal filaments (x1000).

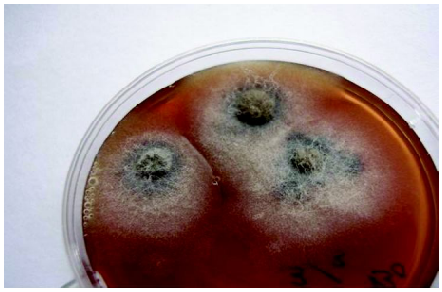

Figure-4: Darkly pigmented fluffy fungal colonies on blood agar.

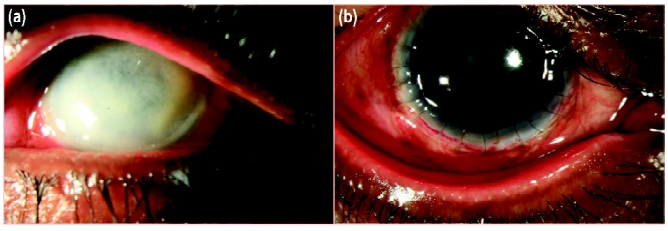


Figure-5: Slit-lamp photograph of a fungal keratitis showing (a) large size infiltrate (b) after therapeutic penetrating keratoplasty

identification include characteristic growth (rate of growth, texture, pigment-reverse and obverse) and sexual and asexual spores. Recently, molecular methods have been introduced for fungal species identification. *Candida spp.* would require employment of biochemical tests for species identification. Automated methods such as API Candida (bioMérieux, France) are also available.

**Molecular Methods**

Polymerase chain reaction (PCR), the most versatile molecular method offers a means to rapidly detect presence of organisms that are difficult to culture. However, PCR does not distinguish viable from non-viable organisms. In an experimental *Fusarium* keratitis study in rabbits, compared to gold standard of culture, PCR (targeting *Fusarium* cutinase gene) was 89% sensitive and 88% specific.[34] The study noted PCR positivity in ulcers that were clinically healed and culture negative, thus undermining the relevance of positive PCR results in healed or healing ulcers. Its role in diagnosis for clinical samples that may contain transient commensal fungi is also controversial.[35]

**Histopathology**

Though microbiologic evaluation of corneal scrapings remains the mainstay of diagnosis in fungal keratitis, the pathobiology of fungal keratitis is better understood by the histopathologic examination of the excised tissues. The outcome of mycotic keratitis depends ultimately on the interplay of agent (virulence, resistance to drugs, and toxicity) and host factors (predisposing factors, inflammatory response, and hypersensitivity reactions) in addition to timely diagnosis and appropriate medical treatment.

Mycotic infections are almost always of ulcerative type, manifesting as:

- Epithelial Ulceration: These could be central or paracentral or could result in total sloughing of the epithelium.
- Destruction of Bowman's: Destruction of the Bowman's layer with fragmentation could be absent, focal or total.
- Stromal Inflammation: The inflammation is mostly suppurative with neutrophils. Depending on the duration of infection, treatment received, the extent of stromal thickness, inflammation and necrosis varies. In the early stages the inflammation could be in the anterior two-thirds with satellite lesions in the surrounding stroma. The posterior stroma when affected may show loss of stromal keratocytes due to apoptosis. Later these abscess become confluent and lead to total destruction of stroma with necrosis and perforation. In a few cases there could be predominant deep seated lesions along with anterior chamber exudates and hypopyon.
- Descemet's fragmentation/endothelial exudates.
- Anterior chamber exudates.

**Medical Treatment**

Treatment with antifungal agent may be initiated on the basis of smear result alone. Fungal ulcers are commonly treated empirically. Prompt medical treatment of fungal keratitis may prevent loss of vision. Many chemicals have been tried for the treatment of fungal keratitis. Most of the antifungals, currently available are fungistatic, thereby requiring prolonged treatment. Effective eradication of fungi is frequently difficult because of the deeply invasive nature of the infectious process. The corneal epithelium serves as a barrier to the penetration of most topical antifungal agents. Debridement plays an important role in the management of fungal keratitis.

Currently available antifungal agents can be mainly divided into three groups (Table-3). In addition to systemic and frequent topical application, intracameral and intracorneal injection of antifungal medication has been reported.

**Surgical Treatment**

Fungal keratitis is one of the most frustrating therapeutic problems encountered by an ophthalmologist. It is a surgical disease in most part of the world because of (i) delayed presentation, (ii) atypical clinical presentation, (iii) non-availability of fungicidal agents, (iv) keratitis refractory to medical therapy and (v) progressive thinning and perforation while on medical therapy. Daily debridement works by debulking organisms and necrotic material and

by enhancing the penetration of topical antifungal. Surgical lamellar keratectomy is another method of removing fungal filaments. Approximately one third of fungal infection results in either medical treatment failure or corneal perforation. The use of N-butyl cyanoacrylate tissue adhesive in the management of corneal thinning and perforation has been reported.[36] The most common surgical procedure reported is therapeutic penetrating keratoplasty (Figure-5). The main goals are: (i) excision of infected tissue, (ii) decrease microbial load, (iii) preservation of structure, and (iv) restoration of vision. The indications are :

1. Keratitis refractory to medical therapy.
2. Progressive thinning
3. Perforation.
4. Advanced keratitis at presentation
5. Undiagnosed keratitis

Table-3: Drugs used for the treatment of fungal keratitis

| Group | Mechanism of action | Antifungals | Route (strength) of administration | Spectrum of activity | Toxicity | Remarks |
|---|---|---|---|---|---|---|
| Polyenes | Polyenes bind preferentially to fungal ergosterol, thereby altering membrane permeability and disrupting the fungal cell. | Amphotericin B | 1. Topical (0.15%) solution<br>2. Subconjunctival<br>3. Intracameral (10µg/0.1ml)<br>4. Intrastromal<br>5. Collagen shield soaked with amphotericin B (0.5%) | 6. *Candida spp.*<br>7. *Aspergillus spp.* | 1. Chemosis,<br>2. Burning,<br>3. Epithelial clouding,<br>4. Punctuate epithelial erosion,<br>5. Tissue necrosis at the injection site. | Not available as an ophthalmic preparation. |
| | | Natamycin | • Topical (5%) suspension | • *Fusarium spp.*<br>• *Aspergillus spp.*<br>• *Curvularia spp.*<br>• *Candida spp.* | • Punctate keratitis | Most commonly used, commercially available topical antifungal |
| | | Nystatin | • Topical (50,000units/ml) solution | • *Candida spp.* | | Poor ocular penetration |
| Imidazole | The imidazole derivatives inhibit the biosynthesis of ergosterol, the main sterol in membranes of fungi. These agents also affect the synthesis of triglycerides and phospholipids. Changes in oxidative and peroxidative enzyme activities, leading to an intracellular buildup of toxic concentrations of hydrogen peroxide, may contribute to the observed deterioration of subcellular organelles and to cell necrosis. | Ketoconazole | (a) Systemic (200-600mg/day)<br>(b) Topical (1-2%) solution | • *Candida spp.*<br>• *Aspergillus falvus*<br>• *Curvularia spp.* | Care needed in patients with previous hepatic disease | Poor *in vitro* activity *vs. Aspergillus fumigatus* and *Fusarium spp.* |
| | | Itraconazole | • Systemic (200-400mg/day)<br>• Topical (1-2%) ointment | • *Aspergillus spp.*<br>• *Candida spp.*<br>• Dematiaceous fungi | Care needed in patients with previous hepatic disease | Poor *in vitro* activity *vs. Fusarium spp.* |
| | | Econazole | • Topical (1%) solution | • Filamentous fungi | Ocular irritation | Not available as an ophthalmic preparation. Less effective against *Candida spp.* |
| | | Miconazole | • Topical (1%) solution<br>• Subconjunctival (10mg) | • Yeast<br>• Filamentous fungi | Conjunctival injection, punctuate epithelial corneal erosion | Not available as an ophthalmic preparation |
| | | Clotrimazole | • Topical (1%) solution, | • Broad-spectrum antifungal | Ocular irritation, punctuate keratopathy | Not available as an ophthalmic preparation |
| | | Fluconazole | • Systemic (200mg/day)<br>• Topical (0.2%) solution<br>• Subconjunctival | • *Candida spp.* | ---- | Poor *in vitro* activity *vs. Aspergillus spp.* and *Fusarium spp.* |
| | | Voriconazole | • Topical (0.1%) solution<br>• Systemic (400mg/day)<br>• Intrastromal (50µg/0.1mL) | • *Aspergillus spp.*<br>• *Candida spp.*<br>• *Fusarium spp.*<br>• *Curvularia spp.*<br>• *Scedosporium spp.* | ---- | Not available as an ophthalmic preparation |
| | | Posaconazale | • Systemic (400mg/day) | • *Candida spp.*<br>• Filamentous fungi | ---- | Not available as an ophthalmic preparation |

| Group | Mechanism of action | Antifungals | Route (strength) of administration | Spectrum of activity | Toxicity | Remarks |
|---|---|---|---|---|---|---|
| Fluorinated Pyrimidines | Flucytosine is deaminated to 5-fluorouracil, which is then phosphorylated and incorporated into RNA; protein synthesis is consequently impaired. A mechanism of action via inhibition of DNA synthesis is an alternative explanation. | Flucytosine | 1. Topical (1%) solution<br>2. Systemic (150mg/kg/day) | 3. *Candida spp.* | Gastrointestinal toxicity | Resistance can be induced with prolonged therapy |
| Alyllamines | Alyllamines Inhibits squalene epoxide, an essential step in fungal ergosterol synthesis | Terbinafine | (a) Systemic (150mg/kg/day) | (b) *Candida spp.* | ---- | Synergistic activity with triazole compounds |
| Echinocandins | The echinocandins blocks the synthesis of a major fungal cell wall component, 1-3- ß-D-glucan, presumably via inhibition of 1,3- ß-D-glucan synthase. | Micafungin | Topical (0.1%) solution | *Candida spp.*, *Aspergillus spp.* | ---- | Not available as an ophthalmic preparation |
| | | Caspofungin | Topical (1%) solution | *Candida spp.* and *Aspp.* | ---- | Not available as an ophthalmic preparation |
| | | Anidulafungin | ---- | *Candida spp.*, *Aspergillus spp.* | ---- | |

## CONCLUSION

In summary, the diagnosis and treatment of fungal keratitis can be quite challenging. Prompt diagnosis and appropriate and timely management are required to increase the chance of cure.

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