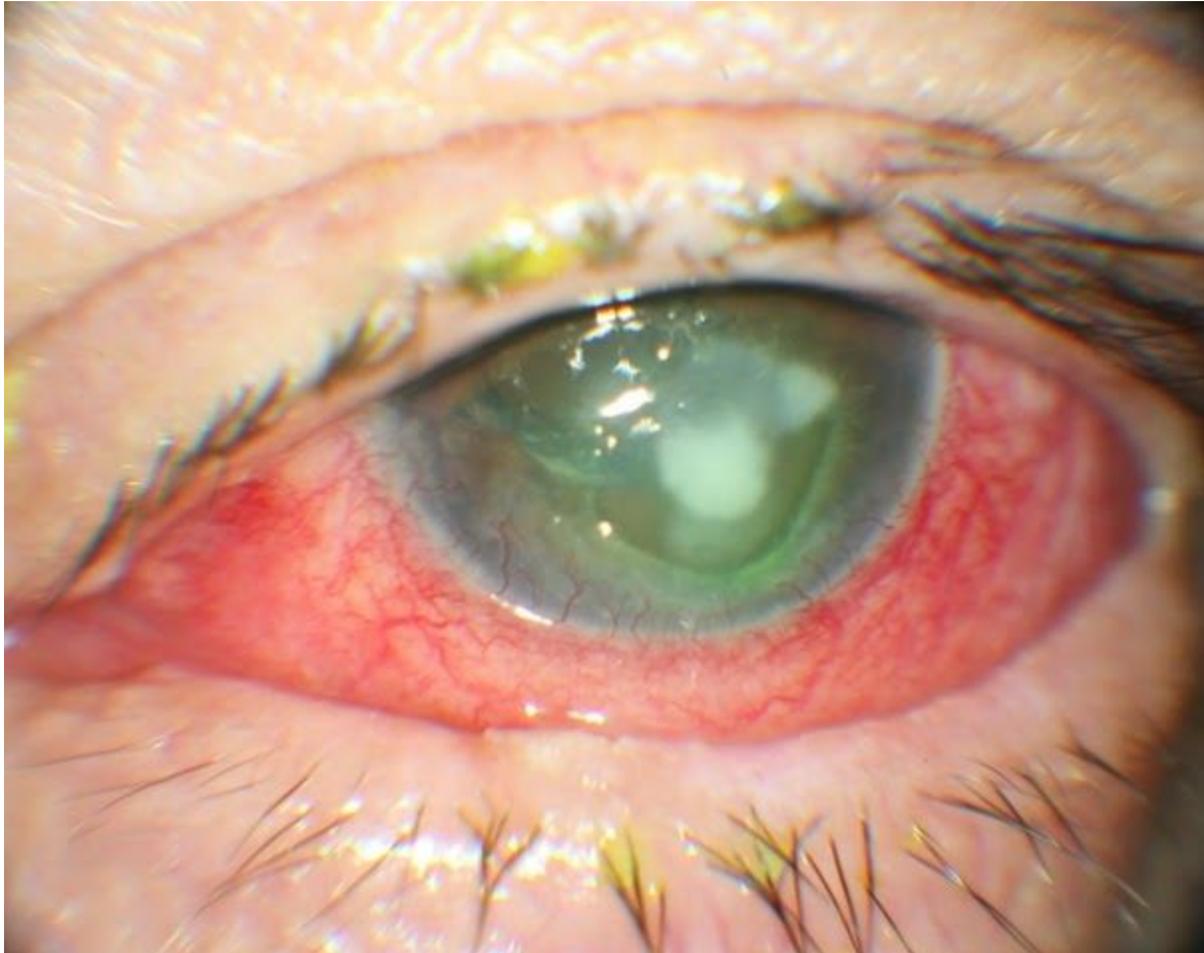


# Fungal Keratitis

Fungal keratitis or keratomycosis refers to an infective process of the cornea caused by any of the multiple pathologic fungi capable of invading the ocular surface. It is most typically a slow, relentless disease that must be differentiated from other types of corneal conditions with similar presentation; especially its bacterial counterpart, which accounts for the majority of the microbial corneal infections.



## Disease Entity

Fungal Keratitis

## Disease

Fungal keratitis is a serious ocular infection with potentially catastrophic visual results. Caused by any of the many species of fungi capable of colonizing human tissue, it occurs worldwide and its incidence is increasing in frequency.

## Etiology

The list covers many fungi including but not limited to yeasts of *Candida* spp., filamentous with septae such as *Aspergillus* spp., *Fusarium* spp., *Cladosporium*, spp., *Curvularia*, and non septated such as *Rhizopus*. Bare in mind that any agent capable of infecting humans is a potential infectious agent, especially if the host has a debilitating disease.

## Risk Factors

Risk factors include trauma, ocular surface disease, and topical steroid use. Risks and type of fungi also might vary by geographic location and climate.[1] [2] [3] [4] [5] [6] [7] In warmer climates the rule is that the most common organisms are filamentous fungi, like *Fusarium* spp and *Aspergillus* spp. with a strong relationship to trauma. Reports from Brazil show the most common isolates in descending order were *Fusarium* spp in 67%, *Aspergillus* spp in 10.5%, and *Candida* spp in 10%. About 40% of the infections were related to trauma.[1]

In the northern USA, corneal infection by fungus was, until recently, more common in debilitated or immunocompromised patients and the causative organism being a yeast, such as *Candida albicans*. Filamentous fungi in these latitudes were then rarely reported. A few years ago a breakout of *Fusarium* keratitis associated with a type of contact lens solution[8] displaced yeasts as the most common fungal corneal infection in some areas. This trend persists in the most recent epidemiological reports. Still they are, in most cases, related to contact lens use.[9] It should be noted that the incidence of contact lens-related fungal keratitis was increasing before the *Fusarium* outbreak.

This new distribution means that we no longer can rely on the geographical distribution only to initiate empirical treatment. Broad-spectrum treatment should be administered once there is a strong probability of a mycotic infection.

## General Pathology

Even though fungi can be classified as a kingdom due to their complexity and unique characteristics, a simple practical classification for ocular infection is used. Under this method, morphology and type of reproductive method define the type of fungi. They are classified for our purpose as yeast, filamentous septated pigmented and non-pigmented and filamentous without septae. Fungi are present worldwide and can be part of the ocular flora. They are eukaryotic with a defined nucleus surrounded by a membrane. They can be either saprophytic, free organisms that subsist on decaying organic matter or pathologic and require a living host for perpetuation.

The American Academy of Ophthalmology's Pathology Atlas contains virtual microscopy images of tissue samples with the following:

- *Aspergillus* Keratitis
- Fungal Keratitis

## Pathophysiology

The infection probably starts when the epithelial integrity is broken either due to trauma or ocular surface disease and the organism gains access into the tissue and proliferates. Proteolytic enzymes, fungal antigens and toxins are liberated into the cornea with the resulting necrosis and damage to its architecture thus compromising the eye integrity and function.

## Primary prevention

Wearing safety glasses while gardening will diminish the risk of ocular trauma. Also, general hygiene, proper contact lens care, and avoidance of nonessential steroid use should diminish the probability of mycotic infection.

## Diagnosis

A high degree of suspicion from the physician accounts for early diagnosis and treatment, which are paramount for a successful resolution of the fungal keratitis. Corneal ulcers unresponsive to broad-spectrum antibiotics, the presence of satellite lesions, and scanty secretions in a large ulcer are some signs that should raise flags to the attending professional about the possibility of a mycotic agent.

## History

Blurred vision, redness, tearing, photophobia, pain, foreign body sensations, secretions related to trauma, ocular surface disease and topical steroid use are all important characteristics to ascertain in the history.

## Physical examination

After establishing the patient's general condition, the examiner should look for evidence of ocular surface disease and determine the amount and type of secretions and lid swelling. The upper eyelid should be everted to exclude a retained foreign body. The examiner should measure the size and depth of the lesion as well as the presence of satellite lesions. The intraocular pressure should also be ascertained. Anterior chamber reaction and evidence of hypopyon should also be recorded. Vitreous reaction if present may suggest intraocular spread of the disease.

## Signs

With filamentary fungi, the corneal lesions have a white/gray infiltrate with feathery borders. There might be satellite lesions with a hypopyon and conjunctival injection as well as purulent secretions. Ulcers caused by yeast are plaque-like and slightly more defined, similar to bacterial keratitis.

## Symptoms

Symptoms are similar to any corneal infection including blurred vision, redness, tearing, photophobia, pain, foreign body sensation and secretions. In some cases the lesion are rather

indolent which help to delay the diagnosis and hence delay the treatment. Suspicion should be high in cases of trauma with vegetable matter.

## Clinical diagnosis

Under the slit lamp, early on the lesion might look like an unhealed corneal abrasion with scanty infiltrates and no secretions. With time however, the ulcer develops thicker infiltrates and fuzzy margins. The presence of satellite lesions strongly suggests a fungal infection. Redness and periocular edema are also common. This combined with a history of trauma, especially with vegetable matter, ocular surface disease or chronic use of topical steroids should alert the practitioner to the possibility of a mycotic etiology.

## Diagnostic procedures

Corneal scrapings are taken from deep within the lesion with a surgical blade or sterile spatula. To perform a corneal biopsy, a dermatological 2mm punch can be used.

## Laboratory test

For a definitive diagnosis, scrapings taken from deep within the lesion should be made and inoculated in Sabouraud agar. The shortcoming is that it can take up to 3 weeks to grow and identify the organism. For a faster result, smears with special stains such as Gomori, PAS, acridine orange, calcofluor white or KOH should be performed. The drawback is that not all laboratories have these stains available, so, again we might need to rely on the patient's evolution and the physician's clinical acumen. If all labs and cultures are negative, corneal biopsy should be considered to obtain a specimen.

## Differential diagnosis

Fungal infections can mimic any microbial keratitis secondary to other causes: Bacteria, which is the most common cause of corneal infections; Acanthamoeba, related to swimming with contact lenses and or the use of tap water in their cleaning; or herpes simplex or herpes zoster for which recurrences are frequent. Other conditions such as a retained foreign body, sterile infiltrates, marginal ulcers due to Staphylococcal hypersensitivity or chronic epithelial defect should also be ruled out. Again, a high index of suspicion is important in the diagnosis of fungal keratitis.

## Management

In general, management consists of medical therapy with the use of topical and/or systemic anti-fungal medications alone or in combination with surgical treatment.

## General treatment

Topical antifungals, either commercially available or compounded from systemic preparation into eye-drops are the backbone for the management of fungal keratitis. In resistant cases, the addition

of systemic antifungal have shown effectiveness. If those treatments fail, then conjunctival flaps , lamellar or penetrating keratoplasty might be needed.

## Medical therapy

Fungal ulcers are inherently difficult to treat. The diagnosis is often delayed and medications available for ocular therapy are limited and are deficient in their ability to penetrate deep into the cornea. The mainstay of treatment is the use of antifungal drops but only a polyene, natamycin 5%, is FDA approved and commercially available for topical ocular use. Also, due to the rarity of the diagnosis it is sometimes available only as a special order. Furthermore, the complexity of the disease and possible visually devastating outcomes require a rather aggressive approach to its treatment. Hence, many other antimycotics are used to fight this infection. These compounded eye drops are made by diluting the intravenous medication into concentrations that provide enough medication to eradicate the organism while being tolerated by the eye.

Prior to the development of natamycin the most commonly used antifungal was amphotericin b, a polyene, in a 0.15% dilution in sterile water (one 50mg vial of amphotericin b diluted in 30cc sterile water gives a 0.166% dilution). It is still used today alone and in combination with natamycin with relatively good results. Since they both are readily available, they are both a good choice as initial therapy.

Voriconazole, a triazole antifungal agent derived from fluconazole, can be used either topically at 1% dilution, orally at 400 mg twice a day and even has being injected in the corneal stroma around the fungal lesion (50 micrograms/0.1 ml)[10] [11] [12]

Oral posaconazole, a new generation triazole, has been successful eradicating deep infections of resistant *Fusarium*[13] Subconjunctival antifungals are not generally used because they produce severe pain and some might even induce tissue necrosis.

Other antifungals available include the azoles like miconazole, clotrimazole ketoconazole, posaconazole, and fluconazole and the echinocandin antifungal agents caspofungin, and micafungin. The echinocandins are not active against *Fusarium*.

## Medical follow up

All corneal infections should be followed daily until there is a marked improvement. Since fungal infections run a protracted course, their follow up is longer and after a few days the interval between evaluations increases according to its progress. Complete healing might take weeks and even months. The intraocular pressure should be closely monitored during the episode. It should be noted that epithelialization does not necessarily mean that the ulcer is healing. In fact it might hinder the penetration of the fungicide. Confocal microscopy might be an effective additional method to follow the success or failure of the therapy. It does so by direct examination of the organism, inflammation, and corneal stromal cells.[14]

## Surgery

Periodic debridement is commonly used in the management fungal keratitis. The procedure removes necrotic tissue and diminishes the organism load but mostly it enhances the penetration of the drugs. It can be performed every 24 to 48 hours.

If everything fails, a conjunctival flap might deter the infection. If there is no response, then a lamellar or penetrating keratoplasty could be needed. If there is a perforation, a patch graft or a therapeutic transplant should be performed. The infected cornea should be sent for cultures and pathological evaluation. It is performed in the usual manner but it should extend about 1 to 1.5mm beyond the margins of the lesion.

## Surgical follow up

Close follow up for at least 2 weeks with topical antimycotics is recommended. Systemic medication may be added as well. If the edges of the specimen are found by pathology to have organisms the use of topical and systemic antifungals should be extended.

## Complications

Adverse results range from mild to severe corneal scarring, corneal perforation, anterior segment disruption and glaucoma to endophthalmitis resulting in evisceration.

## Prognosis

The aftermath of fungal keratitis can be dismal . There is severe visual loss in 26% to 63% of patients. Fifteen to twenty percent may need evisceration. Penetrating keratoplasty is required in 31 to 38% of cases.<sup>[1][15]</sup>

## Additional Resources

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