Fungal keratitis

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Purpose of review

Throughout the world, fungal keratitis is a leading cause of ocular morbidity. The purpose of this review is to discuss the recently published literature in relation to the epidemiology, etiology, diagnosis, and therapy of fungal keratitis.

Recent findings

Globally, the incidence of keratomycoses and systemic mycoses is rising. Current therapies are often ineffective. Ongoing research toward rapid diagnosis and specific drug therapy could minimize the morbidity caused by this preventable disease. New antifungal drugs, including voriconazole, have been applied recently for the treatment of keratomycosis.

Summary

The incidence of fungal keratitis is on the rise in the densely populated continents of Asia and Africa. Filamentous fungi are the most frequently reported pathogens. Polyene antifungal antibiotics, the first-line therapy in fungal keratitis, are not effective in severe keratomycosis. Imidazole derivatives such as voriconazole and echinocandin may be the better choice in the future.

Keywords

fungal keratitis, mycotic keratitis, keratomycosis, antimycotic drugs, voriconazole

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Abbreviations

KOH	potassium hydroxide
PCR	polymerase chain reaction
PHMB	polyhexamethylene biquanide

1040-8738

Introduction

According to the World Health Organization, corneal diseases are a major cause of vision loss and blindness, second only to cataract in overall importance [1]. It is estimated that ocular trauma and corneal ulceration result in 1.5 to 2 million new cases of corneal blindness annually.

Epidemiology

Fungal keratitis is a major blinding eye disease in Asia. One report from South India found that 44% of all central corneal ulcers are caused by fungi [2]. This high prevalence of fungal pathogens in South India is significantly greater than that found in similar studies in Nepal (17%), Bangladesh (36%), Ghana (37.6%), and south Florida (35%) [3–7]. In China, the incidence of fungal keratitis has increased during the past decade [8]. In temperate climates, such as Britain and the northern United States, the incidence of fungal keratitis remains very low [9,10].

Predisposing factors

Local predisposing factors include trauma, contact lenses, and topical steroids.

Trauma

Injury to the cornea is the leading cause of microbial keratitis, particularly fungal keratitis. A history of corneal trauma with vegetable matter or organic matter is reported in 55 to 65% of fungal keratitis (11,12••,13]. A study from the northern United States reported trauma as the inciting event in only 8.3% of cases [14]. In the southern United States, trauma was identified as a principal risk factor in 44% of children who had microbial keratitis and 27% among 227 cases of microbial keratitis reported in a nonreferral county practice in southern California [15,16].

Contact lenses

Several case reports published recently have identified contact lens wear as a risk factor for fungal keratitis in industrialized countries (29%) [17]. Patients wearing any type of contact lens can get fungal keratitis [18].

Topical steroid use

Many ophthalmologists identify topical steroids as the principal risk factor in enhancing ocular fungal growth. Steroid use as initial therapy was reported in 1 to 30% of patients having microbial keratitis [11,12••,13,19]. However, several other large studies of infective keratitis reported from tropical countries do not support steroid use

as a risk factor for the development of suppurative keratitis [11,12••,13].

Other factors

Other disorders, including corneal surface disorders, dry eye, bullous keratopathy, and exposure keratitis, are associated with the development of suppurative keratitis [14,20•]. Recently, several case reports of fungal keratitis after photorefractive keratectomy and Lasik have been published [18,21•,22,23].

As for systemic factors, the incidence of fungal keratitis is not particularly high in immunocompromised patients and those with diabetes [11,12••,13].

Commonest etiologic agents

Filamentous fungi form the major etiologic agents of fungal keratitis. *Fusarium* species (37–62%) and *Aspergillus* species (24–30%) have been implicated as main pathogens. Dematiaceous fungi are the cause of 8 to 16.7% of cases of fungal keratitis [7,11,12••,19,24]. Most filamentous fungi associated with corneal ulceration in the tropics are found widely within the environment. Chang *et al.* [25] from Taiwan have reported that *Fusarium* species are common plant pathogens, particularly in corn crops or onion fields.

Yeast can also cause keratitis. Gopinathan *et al.* [19] from India have reported *Candida* as a rare fungal corneal pathogen (0.7%). In a series of 24 patients from Wills Eye Hospital, Philadelphia, *Candida* was identified in 45.8% of cases of fungal keratitis; this probably represents the only study reporting *Candida* as the commonest etiologic agent of fungal keratitis [26].

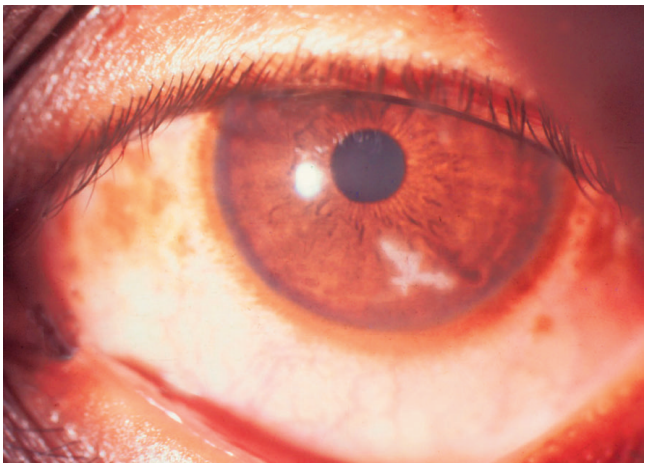
Unlike the experience of bacterial keratitis, for the past two decades the spectrum of fungal pathogens causing fungal keratitis has not changed significantly [11,12••,13].

Clinical features

Bharathi *et al.* [12••] reported a large series of fungal ulcers (1095) occurring in South India. In this study, male patients were affected more commonly than female patients. Approximately 65% of patients were in the age group of 21 to 50 years.

For several decades, the fungal ulcer has been described as indolent and dry, with a leathery, tough, raised surface [12••,27,28••]. In this author's experience in treating several hundred fungal ulcers, the clinical features do not always correlate with classic textbook descriptions. The early fungal ulcer will appear like a dendritic ulcer of herpes simplex virus origin (Fig. 1). The signs of inflammation will be minimal in comparison with bacterial keratitis. The absence of lid edema is a common feature. The infiltrates appear grayish-white or yellowish-white, and the base of the ulcer is often filled with soft, creamy, raised exudates, making it very easy to scrape the material even with a Kimura spatula.

Figure 1. Very early fungal keratitis resembling dendritic ulcer



Feathery borders or hyphate edges (Fig. 2) are seen in 70% of patients, and satellite lesions in 10% of patients, with fungal keratitis [12••]. Hypopyon is present in 55% of cases [12••]. Fungal keratitis due to dematiaceous fungi is characterized by brown or black pigmentation on the surface of the ulcer (Fig. 3), which appears dry, rough, and leathery; it can be difficult to obtain scrapings for culture using a spatula. An immune ring (Fig. 4), satellite lesions, and posterior corneal abscess are seen infrequently (Fig. 5). Advanced *Fusarium* keratitis may progress to endophthalmitis [29•].

Laboratory diagnosis

Laboratory diagnosis can be made by means of smear, staining, fungal culture, polymerase chain reaction, and confocal microscopy.

Figure 2. Fungal keratitis showing yellowish-white base with typical feathery borders

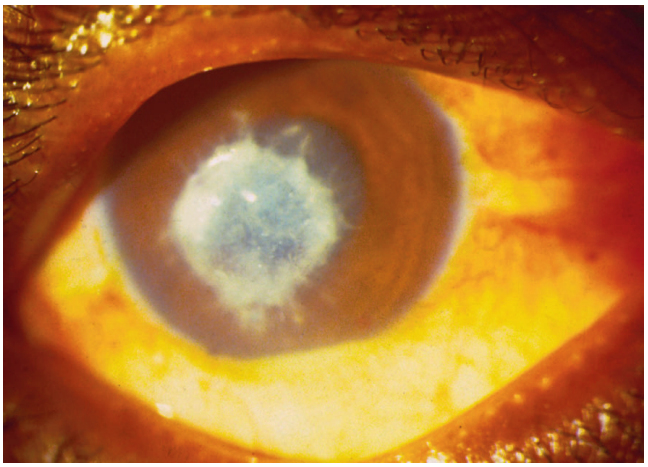


Figure 3. Pigmented fungal keratitis of more than 2 weeks

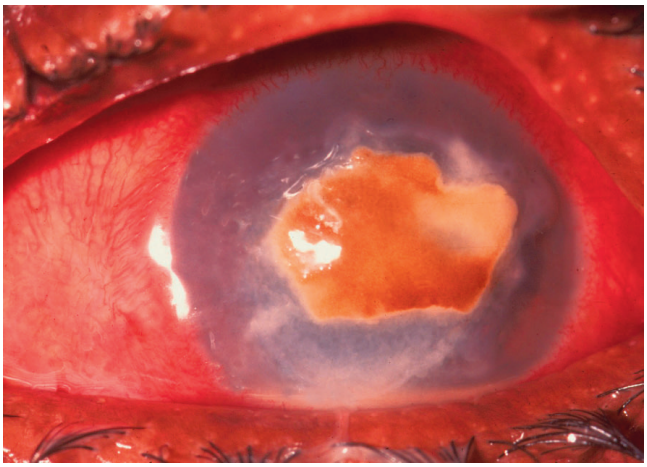
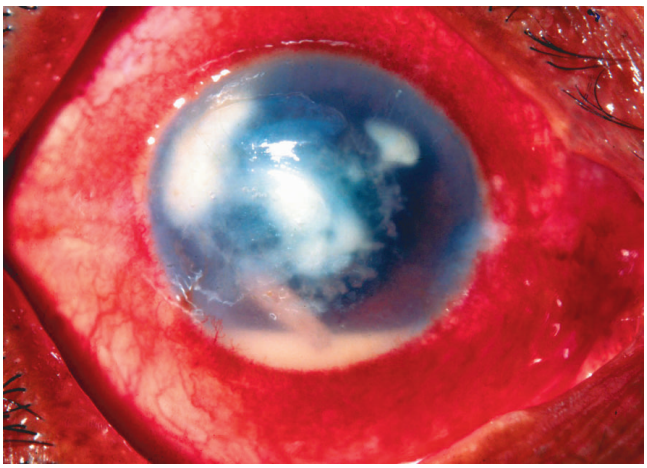


Figure 5. Satellite lesions and posterior corneal abscess in a case of fungal keratitis



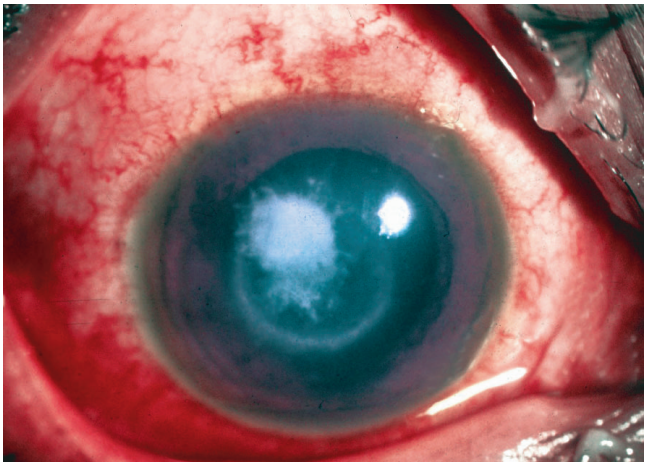
Smear

Direct microscopic evaluation is the most valuable and rapid diagnostic tool for the detection of fungal filaments in corneal scrapings. Giemsa stain and Gram stain are equally sensitive in detecting fungal elements [30]. Thomas [28••] has highlighted the sensitivity of various stains. Gram stain will identify fungal species in 45 to 73% of cases, and Giemsa will identify fungi in 66%. Lactophenol cotton blue has a sensitivity of 70 to 80%, Grocott methenamine silver staining of as much as 89%, and calcofluor white of 80 to 90%.

There have been differing reports on the sensitivity of the potassium hydroxide (KOH) smear. A retrospective study [12] of 3183 corneal ulcers reported that the sensitivity of the 10% KOH wet mount (Fig. 6) was higher (99.23%) than that of the Gram stained smear (88.73%) (Fig. 7) in the detection of fungal keratitis. Another study from South India reported equivalent sensitivities when 10% KOH smear (90%) was compared with calcofluor white (91%) (24). Conversely, Liesegang and Forster [7] and Forster and Rebell [31] have reported much lower sensitivities (5 to 33%) when using KOH .

In our experience, 10% KOH wet mount is simple, cheap, rapid, and easy to interpret even by ophthalmic technicians. It is an ideal method for practice in tropical and developing countries.

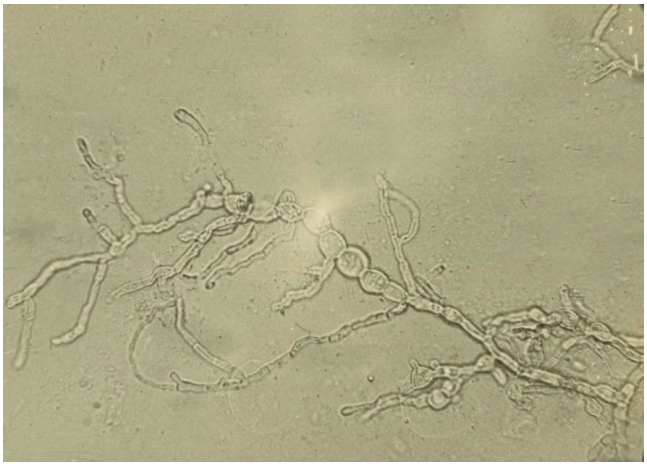
Figure 4. Immune ring, with raised surface and hyphate edge, in a case of fungal keratitis



Fungal culture

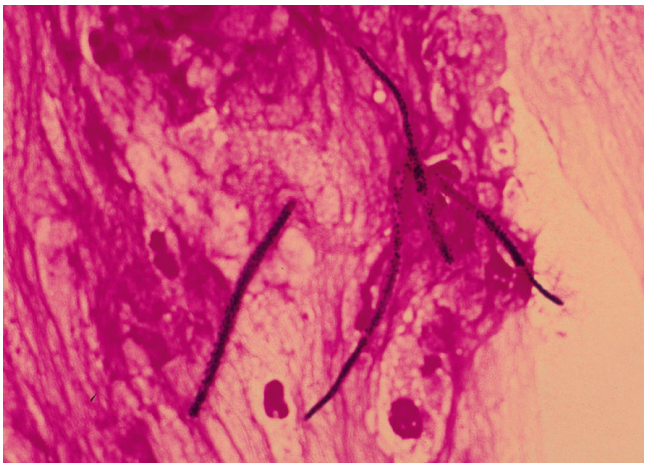
Fungus grows within 48 to 72 hours in blood agar and Sabouraud dextrose agar (Figs. 8 and 9) kept at room temperature (27°C). The rate of positive culture in microbial keratitis ranges from 52 to 68% but depends on the severity of the ulcer and the criteria established for positive culture [5,12••,13]. The anterior chamber tap is extremely useful in the management of ocular infections confined to the anterior segment, deep keratitis, and posterior corneal abscess. The procedure should be performed under strict aseptic conditions [32].

Figure 6. Filamentous fungi



10% potassium hydroxide, direct smear (×450 magnification).

Figure 7. Branching fungal hyphae



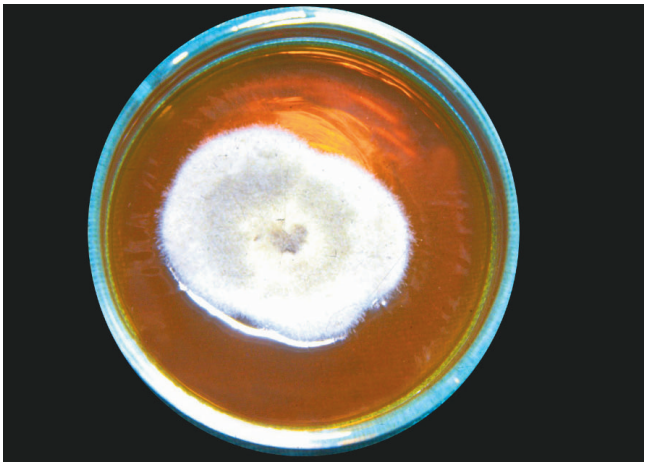
Gram stain cytoplasm stained with crystal violet, (×450 magnification)

New diagnostic tools

Although polymerase chain reaction (PCR) and confocal microscopy are being used as new rapid diagnostic methods; they are not available in areas where fungal keratitis is highly prevalent. Alexandrikis *et al.* [33] have diagnosed *Fusarium* keratitis in an animal model using PCR. Gaudio *et al.* [34] have reported that PCR and fungal culture reports matched in 22 (74%) of 30 scrapings from infected corneas. The PCR assay used in this study requires 4 hours to generate results; this is significantly faster than the 2 days to 2 weeks required by culture technique.

Confocal microscopy is a relatively new, noninvasive technique for imaging the cornea in normal and diseased states [35]. Avunduk *et al.* [36•] found that confocal microscopy in experimentally induced *Aspergillus fumigatus* keratitis in rabbits was more sensitive than culture on days 14 and 22 in treated and untreated control rabbits.

Figure 8. *Fusarium* spp.



Grown in Sabouraud dextrose agar. The colony is soft, fluffy, and pearly white.

Figure 9. *Aspergillus flavus* (greenish yellow) and *Aspergillus fumigatous* (bluish green)

Grown in Sabouraud dextrose agar. The colony is rough and dry with rugae formation.

Medical therapy

Currently, the therapy of fungal disease of the eye is unsatisfactory. The antifungal agents available today are mostly fungistatic, requiring a prolonged course of therapy. Although models of *Aspergillus* and *Candida* have been established, there are no reliable animal models of *Fusarium* keratitis. Fungi considered to be ocular pathogens are rarely encountered among the systemic mycoses. Thus, the therapeutic principles valid for systemic fungal infections may not apply to the cornea [37].

Polyenes

The polyenes include natamycin and amphotericin B.

Natamycin

Natamycin, available as 5% suspension (Natacyn, Alcon, Texas, USA; Natamet Sun Pharmaceuticals, Mumbai, India; Nata–Cipla Limited, Mumbai, India) is considered the drug of choice for filamentous fungi [37]. Because of poor penetration, it is effective only in nonsevere superficial keratitis. Prajna *et al.* [38••] conducted a

prospective study comparing the efficacy of natamycin 5% and econazole 2% in 112 cases of culture-proved fungal keratitis and found no statistically significant difference between the two drugs. Moreover, natamycin is very costly; the supply is erratic, and it is difficult to obtain in the third world.

Amphotericin B

Amphotericin B is available as a systemic preparation. To prepare the topical form, the compound is diluted with dextrose or distilled water to arrive at a 0.15 to 0.5% concentration (Fungizone, Sarabai Piramol, Vadodara, India). It can also be used through the subconjunctival (10 μg), intracameral (5–7.5 μg), intravitreal (10 μg) and intravenous routes (0.1 mg/kg body weight). The penetration of topically applied amphotericin B is poor in cornea with intact epithelium. The spectrum of activity of amphotericin B covers *Candida* species and *Aspergillus* species. It is not effective against *Fusarium* species [39].

Azole compounds

The azole compounds include triazole, clotrimazole, the imidazoles, fluconazole, and voriconazole.

Triazole

Econazole 1% in arachis oil is available as an ophthalmic preparation in India (Aurozole, Aurolab, Madurai, India). Prajna *et al.* [38••] have found that the effect of this drug is equal to that of natamycin against filamentous fungi.

Clotrimazole

Clotrimazole is also available as a 1% topical preparation as drops and in ointment form (Auroclot, Aurolab, Madurai, India) (Nistin-C, Jawa Pharmaceuticals, India). Mselle [40] treated 12 patients with proven fungal keratitis with clotrimazole but suggested that clotrimazole as monotherapy is not an ideal choice.

Imidazoles

Whereas the imidazoles, miconazole and ketoconazole, have less systemic toxicity, they are inferior to amphotericin B [41]. Because of relatively reduced systemic toxicity and better corneal penetration, these compounds can be used systemically for keratomycosis. Thomas *et al.* [28••] over a period of 10 years (1984–1994) treated 330 cultured-proved fungal keratitis cases with ketoconazole, itraconazole, amphotericin B, and natamycin and found that 69% of patients responded to ketoconazole, 66% to itraconazole, 53% to amphotericin B, and 56% to natamycin. In severe keratitis it was less than 60% in all the groups. *Fusarium* is common in this region.

Fluconazole

(Diflucon, Pfizer NC, New York, USA), a fungistatic bitriazole is considered a topical and systemic agent in the treatment of fungal keratitis due to *Candida* and *Aspergillus* [42•]. Schreiber *et al.* [43•] used fluconazole and corticosteroid for experimental *Candida albicans* keratomycosis. However, fluconazole does not show encouraging results against *Aspergillus* species and *Fusarium* species [44]. Panda *et al.* [45•] from India compared the effect of natamycin 5%, polyhexamethylene biquanide (PHMB) 0.02%, 1% povidone iodine, and placebo in experimental *Aspergillus* keratitis in a rabbit model and concluded that PHMB was moderately effective and povidone iodine was not effective.

Voriconazole

A new azole antifungal agent, voriconazole, is derived from fluconazole and shows a broader spectrum of activity against *Candida*, *Aspergillus*, *Scedosporium*, *Fusarium* and *Paecilomyces*. Jeu *et al.* [46••] described the mechanism of action. As with other triazole antifungal agents, voriconazole exerts its effect primarily through inhibition of cytochrome P450–dependent 14α sterol demethylase, an enzyme responsible for the conversion of lanosterol to 14α demethyl lanosterol in the ergosterol biosynthetic pathway. Eighty percent of this drug is hepatically eliminated. Shah *et al.* [47•] conducted an *in vitro* study to determine the activity of voriconazole compared with other polyene and imidazole antifungal agents against corneal isolates of *Scedosporium apiospermum* and found that the minimal inhibitory concentration of voriconazole was 0.5 μg/mL, a concentration lower than that of the other imidazoles.

Under new antifungal drugs, echinocandins are used for systemic mycoses [48•]. The target of the echinocandins is the synthetic cell wall enzyme complex β-1, 3-D glucon synthase. The antifungal spectrum is restricted to *Candida* species and *Aspergillus* species and is not active against *Fusarium* species.

Surgical therapy

The use of *N*-butyl cyanoacrylate tissue adhesive in the management of corneal thinning or perforation associated with active fungal keratitis has been reported [49•]. In a study of 73 patients, 63% showed resolution of infiltration with scar formation. Xie *et al.* [50] have tried lamellar keratoplasty. Amniotic membrane transplantation promotes healing and reduces inflammation in suppurative keratitis. Penetrating keratoplasty is the ideal method to treat nonhealing fungal keratitis threatening perforation. Structural integrity and eradication of sepsis is achieved in 80 to 90% of eyes and graft clarity in 36 to 89% [51,52,53•].

Conclusion

Fungal keratitis is responsible for a significant burden of blinding disease in the developing world. Current treatment methods frequently fail to preserve or restore vision after fungal keratitis. Although emerging antifungal agents show promise, therapeutic gaps will probably persist, and further development is necessary. Priorities

should be given to develop and undertake drug trials against filamentous fungal keratitis. Basic research about the role of cytokines in corneal inflammation and tissue destruction should be encouraged.

Acknowledgments

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- •• Of outstanding interest

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