Published in final edited form as:
Curr Fungal Infect Rep. 2013 September 1; 7(3): 209–218. doi:10.1007/s12281-013-0150-110.1007/s12281-013-0150-1.

Current Thoughts in Fungal Keratitis: Diagnosis and Treatment

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Abstract

Fungal keratitis remains a challenging and often elusive diagnosis in geographic regions where it is endemic. Marred by delays in diagnosis, the sequelae of corneal fungal infections, though preventable, can be irreversible. Recent studies and advances in the arena have broadened the approach and treatment to mycotic keratitis. This review will discuss current diagnostic modalities of fungal keratitis and will particularly focus on treatment regimens. It will also explore future therapeutic models and critique the potential benefit of each.

Keywords

Fungal; Keratitis; Fungal keratitis; Mycotic keratitis; Antifungal; Natamycin; Mycotic; Fusarium; Eye infections; Corneal infections

Introduction

Keratitis is an inflammation of the layers of the cornea. It is most commonly associated with bacterial or viral microorganisms that invade into the corneal stroma, resulting in inflammation and ultimately, destruction of these structures.

Of the organisms that cause keratitis, fungi remain one of the most elusive and challenging organisms to diagnose and treat. It has also been shown that infection with fungal keratitis (FK) can be more virulent and damaging compared to that of a bacterial origin. Fungal keratitis in previous retrospective analyses was shown to be more likely to perforate the cornea than bacterial keratitis (OR = 5.86, 95 % CI, 2.06–16.69) and lead to irreversible changes. [1,2] Ocular trauma is a major predisposing factor for fungal keratitis and most cases are reported from developing countries such as India and Ghana.[1,3,4] Microorganism invasion occurs secondary to alterations of the corneal surface, resulting in potential spaces for organisms to track deeper into underlying layers. This invasion leads to a mostly innate and adaptive immune-mediated inflammation, resulting in subsequent tissue necrosis of the surrounding area. As fungi penetrate into the stromal layers of the cornea, there appears to

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Conflict of Interest
Zubair Ansari declares no conflicts of interest.
Darlene Miller declares no conflicts of interest.
Anat Galor declares no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

be a reactive innate and adaptive immune response that occurs which consequently leads to further tissue damage, scarring, and therefore, opacification of the cornea. The exact mechanisms of this process, including the specific inflammatory mediators, however, have not yet been fully elucidated. [5–7] If microorganisms penetrate deeper into the corneal stroma, through Descemet's membrane, and into the anterior chamber or sclera, eradication of the organism becomes tremendously difficult. This invasion followed by the subsequent tissue damage that follows is particularly devastating as it can disrupt the visual axis. Early diagnosis and treatment of fungal keratitis is therefore imperative to prevent visual threatening complications. [5]

Epidemiology*(See Table 1-1 for most common agents associated with fungal keratitis)*

Filamentous fungi, such as *Fusarium* and *Aspergillus*, and yeast-like fungi, such as *Candida*, are most commonly associated with keratitis. Many other species have also been robustly reported, ranging from *Culvaria* and other phaeohyphomycetes, *Scedosporium apiospermum* and *Paecilomyces*.[8] The prevalence of specific agents of fungal keratitis appears to have a strong geographic influence. *Candida albicans* and related fungi tend to be implicated when complicated chronic ocular surface disease or systemic illnesses such as diabetes mellitus or immunosuppression, are present. [9]

Fungal keratitis is historically associated with trauma with vegetative matter or objects contaminated with soil in both developed and developing countries. However, as farming has become more industrialized and the use of contact lenses has become more popular in the US, wearing of refractive contact lenses is the presumed risk factor in 37 % of patients as compared to ocular trauma for 25 % of patients. [10] Conversely, in developing countries such as India and Thailand, fungal keratitis is mainly attributed to ocular trauma, and contact lens associated FK is a rare cause of infection. [11] In these countries, fungal keratitis comprises up to 40 % of microbial keratitis cases.[3,12] In India, the estimated incidence of fungal keratitis is 113 per 100,000.[13] with *Aspergillus* being the most causative etiology.[14]

In the United States, 30,000 new cases are reported annually.[15] *Candida* and *Aspergillus* are the most common causes; however, *Fusarium* is more common in South Florida.[14,16–19]

An outbreak of *Fusarium* keratitis was associated with the use of the contact lens cleaning solution ReNu with MoistureLoc (Bausch & Lomb, Rochester, NY). It was proposed that this solution lost its fungistatic property as it interacted with its Bausch & Lomb plastic container at elevated storage temperatures.[20] Following removal of ReNu with MoistureLoc from the US market, the number of *Fusarium* keratitis cases returned to epidemiological baseline levels; however, the number of other filamentous fungal keratitis cases seems to have increased among contact lens wearers.[10]

Clinical features and diagnosis

Patients with keratitis usually report a sudden onset of pain, photophobia, discharge and reduced vision in a patient with an inflamed eye and an opacity on the surface of the cornea suggestive of an ulcer. Historically, fungal keratitis was thought to be a suppurative corneal lesion with a dry, raised ulcer with crenate (having a margin with low, rounded or scalloped projections), speculated (spikes or points on the surface) or pseudohyphate borders, satellite lesions, hypopyon (leukocytic exudate in the anterior chamber of the eye) or posterior chamber endophthalmitis with progressive shallowing of the anterior chamber, and failure to respond to antibacterial treatment. These guidelines were based on observations in 25 patients with confirmed microbiology for fungal keratitis.[21]

However, the diagnostic validity of these traditional features has been challenged in recent years, and the utility of clinical diagnosis alone can be unreliable. In one study, clinical examiners correctly predicted the presence or absence of microbial recovery in 79 (76 %) of 104 ulcerative keratitis cases and successfully distinguished among bacterial, fungal, and amebic keratitis for 54 (73 %) of 74 culture-positive infections. However, only 31 (42 %) were subcategorized properly, suggesting the notion that although infections can be detected, overlapping clinical features of the etiologic agents of keratitis makes it difficult to distinguish one from another.[22]

Therefore, tissue sampling and culture continues to be an imperative utility in the diagnosis of fungal keratitis. Because of predilection of fungi to penetrate into deeper layers of the cornea, tissue swabbing is usually inadequate in confirming a fungal agent. At this time, a corneal scraping using a surgical bladed or platinum spatula is recommended to obtain a tissue specimen. Yet a recent study showed that excessive scraping should be avoided as scarring may occur and thus worsening the best corrected visual acuity at 3 months. [23] In contact lens wearers, lens, containers, and lens solution may also be used for sampling.

The common approach in patients with suspected infectious keratitis is to begin with a Gram stain of the corneal scraping material. Studies have shown the sensitivity of Gram staining to be in the range of 36–50 %.[24] Next, wet preparation of the corneal scraping can be examined by potassium hydroxide (KOH), ink-KOH, lactophenol cotton blue, Giemsa, or calcofluor white. KOH is a rapid and inexpensive way to detect fungi. It has a sensitivity of 61–94 % and specificity of 91–97 % of detecting FK in different studies. Lactophenol cotton blue mounts had a sensitivity of 85 % and specificity of 90–91 % in studies.[25,26] Calcofluor white is also mainstay of diagnosis. When combined with Giemsa or KOH stains, sensitivity has been shown to be 96.6 % to 98.3 %, respectively. [25]

Once stains have been conducted, culture remains a necessary diagnostic step in severe corneal ulcers and suspected fungal keratitis. For isolation of fungi and bacteria, blood agar (BA) and chocolate agar (CA) may be used instead of Sabouraud dextrose agar (SDA), which is considered to be the culture medium of choice for fungi. In one study, corneal scraping of 141 patients with microbial keratitis were smeared and cultured in India. BA, CA, and SDA were evaluated for time taken for growth and cost. They found that fungal elements grew on BA in 22/39 (56 %), on CA in 18/39 (46 %), and on SDA in 17/39 (43 %) of patients. They concluded that BA and CA, which are less expensive media than SDA, support the growth of bacterial and fungal elements involved in infectious keratitis. They also added that SDA is unnecessary in the diagnosis of fungal keratitis, as fungal species that can be grown on SDA, such as *Histoplasma*, are not known to be causative agents of fungal keratitis.

However the drawback of using culture as a means of confirming diagnosis is the delay in early identification and treatment. Initial growth occurs within 72 hours in 83 % of cultures and within 1 week in 97 % of cultures.[27] Sometimes it may be necessary to wait for 2 weeks to confirm no growth in culture. However, prompt diagnosis and correct treatment of fungal keratitis are important prognostic factors. One study showed that 9 out of 10 cases of advanced *Fusarium* keratitis failed to respond to the combination therapy with oral fluconazole or ketoconazole, topical natamycin and intravitreal amphotericin B injections and the authors concluded that early diagnosis is important for response to medical treatment.[28] In another study, a delay in diagnosis of fungal keratitis in contact lens wearers (greater than 2 weeks), increased the odds of surgery.[29] By the time the result of culture is available, treatment has already been started based on initial clinical impression and Gram stain of the smear. In addition, a negative culture does not rule out the presumed diagnosis because it is not 100 % sensitive.

Polymerase chain reaction (PCR) has also emerged as a rapid sensitive and specific test for the diagnosis of fungal keratitis. In a retrospective nonrandomized trial, corneal samples of 20 patients with proven fungal keratitis over 10 years were evaluated using Gram stain, culture, and PCR. PCR detected all the samples that were positive by conventional methods. Four samples were positive by PCR and showed negative results by culture and stain. Combination of microscopy and culture gave positive results in 21 of the 27 samples of patients with mycotic keratitis. Stains showed 66.7 % positive results, culture showed 59.3 %, and PCR showed 92.6 %.

The authors further concluded that PCR was also time efficient; the time taken for PCR assay was 4–8 hours whereas positive fungal cultures took 1–35 days.[30] However, it is important to note that PCR remains a sophisticated, and more importantly, an expensive utility. It is not the standard of clinical practice to use PCR in the diagnosis of mycotic keratitis and is currently relegated to research purposes.

Finally, in contrast to the aforementioned invasive sampling techniques, confocal microscopy is a noninvasive technique sensitive for diagnosis of fungal keratitis. Confocal microscopy in vivo uses serial images to create optical sections through the full-thickness of the living cornea. The noninvasive nature of confocal microscopy allows for a rapid technique for visualizing the cornea in its physiologic state. Qualitative confocal microscopy is used to examine microorganisms in vivo and can aid in the diagnosis of infectious keratitis. Bacteria cannot be identified by confocal microscopy, but larger organisms such *Acanthamoeba* and fungal filaments can be seen. [31] In a prospective, double masked, nonrandomized clinical trial, 146 patients with suspected microbial keratitis were evaluated using conventional methods and confocal microscopy. Confocal microscopy was reported to be 93 % (CI 95 %, 85.9–99.6) specific and 89 % (95 % CI 83–95.5) sensitive for diagnosing FK.[32] The results of this study, however, should be interpreted cautiously because confocal microscopy is a subjective diagnostic test, and operator-dependent. Although in this study intraobserver (kappa = 0.795) and interobserver (kappa = 0.6) agreement was good, mastering the interpretation of confocal images requires training. Since FK remains endemic only in certain geographies, it is difficult at most institutions to acquire enough experience to use confocal microscopy with confidence. Factoring in the high expense of this technology further adds to the limitations of microscopy, particularly in low socioeconomic communities.

Medical Treatment (See Table 1-2)

Since the Food and Drug Administration's approval of natamycin in the 1960s, many antifungal agents have been evaluated in experimental animal studies, case series, and a few randomized controlled trials. Each antifungal agent has its benefits and limitations, and careful considerations must be made before selection of an antifungal agent. No one agent has emerged as the best and most cost effective agent. In a systematic review in 2008, two independent reviewers included six randomized, controlled trials and 369 participants overall to compare the treatment effect of itraconazole, miconazole, chlorhexidine, sulphadiazine, econazole, or natamycin on fungal keratitis. The reviewers concluded that these trials had a small sample size and based on current evidence, it is difficult to conclude which medication is the best and the most cost-effective. They recommended a large multicenter randomized controlled trial (RCT) to address this question.[33]

Amphotericin B

Amphotericin B is a well-known macrocyclic polyene active against *Aspergillus* and *Candida* species, and commonly administered as a topical solution. Intracameral administration (delivery of medication directly into the anterior chamber of the eye) has also

been shown to be effective in reducing time to disappearance of hypopyon and final improvement in the treatment of fungal keratitis.[34] It is used as a first line agent of *Candida*-associated keratitis in areas where natamycin is not available.[35] Glaringly, however, it has variable activity against common *Fusarium* species. Furthermore, amphotericin B has poor ocular penetration after intravenous administration and is toxic to human cells at a higher dose. A well-known and serious side effect of intravenous Amphotericin B is a dose-limiting nephrotoxicity. [36] Amphotericin B is also well known to cause punctate epithelial erosions and occasionally a greenish discoloration of the cornea. Given the side effect profile and lack of coverage of *Fusarium* species, amphotericin B is not currently a first line agent in treating fungal keratitis in centers where better options are available.

Natamycin

Natamycin continues to the be first line treatment in fungal keratitis and the first antifungal agent approved for FK.[37] Natamycin is currently considered the most effective medication against *Fusarium* and *Aspergillus*. Natamycin binds preferentially to ergosterol on the fungal plasma membrane and causes localized membrane disruptions by altering membrane permeability.[38] In a controlled trial, 50 consecutive patients were treated with natamycin 5 % eye drops hourly followed by 50 consecutive patients treated with itraconazole 1 % eye drops hourly. The primary efficacy criteria were the physician's judgment of clinical success, cure rate, and the rate of treatment failure. The study showed that in the *Fusarium* specific keratitis subgroup, response to natamycin was better than itraconazole (79 % of patients vs. 44 % of patients) (p=0.02).[39]

Of note, a subgroup analysis of RCTs comparing the BSCVA (best spectacle-corrected visual acuity) and scar size between voriconazole and natamycin-treated patients showed no significant difference between the two agents. However, in voriconazole-treated *Fusarium* cases perforation of the cornea was more likely to occur than in *Fusarium* cases treated with natamycin.[23] Though natamycin tends to be the first line treatment in areas where *Fusarium* is endemic, it is limited by its inability to cover for other fungal organisms such as *Candida*. Furthermore, natamycin can only be given topically, while amphotericin B, miconazole, ketoconazole, itraconazole, and fluconazole can be administered by various routes. This limits the use of natamycin to treatment for superficial fungal keratitis as opposed to deep stromal fungal invasion. The presence of deep lesions may necessitate the addition of systemic therapy, such as subconjunctival or intravenous miconazole, oral ketoconazole, oral itraconazole, or oral fluconazole.[40]

Voriconazole

Voriconazole has been proposed as a good alternative to natamycin with minimal toxicity, particularly since susceptibility studies implied that voriconazole is not only active against filamentous fungi such as *Fusarium*, but also against *Candida*.[41,42] Also, voriconazole has been shown to have a wide therapeutic window in animal studies. [43] In a recent study, topical voriconazole was used as an adjunct to natamycin in FK refractory to topical natamycin along with intrastromal injections of voriconazole. The visual acuity after treatment was better in the topical voriconazole group ($P = 0.008$). Nineteen patients receiving topical voriconazole and 16 patients who were given intrastromal voriconazole healed with therapy. No difference was found between intrastromal versus topical treatment.[2] Finally a review of 40 case-reports showed that voriconazole is safe and effective against the major ocular fungal infections. [43]

It is to be noted, however, that the efficacy of voriconazole as a single agent or initial treatment incurs a significant medical failure risk. A recent retrospective review of all fungal keratitis treated with topical voriconazole was conducted at the Royal Victorian Eye and Ear

hospital between January 2003 and July 2010. Parameters evaluated were determined by final outcomes. A total of 26 cases were treated with voriconazole eye drops during this timeframe. An oral tablet (n = 16, 61.5 %), intracorneal injection (n = 7, 26.9 %), and intracameral injection (n = 2, 7.7 %) was also used. 50 % (n = 13) of overall cases responded to medical treatment. Surgical intervention in the form of penetrating keratoplasty was needed in 11 cases (42.3 %). Two cases (7.7 %) underwent enucleation for severe non-resolving keratitis. It was also shown in the study that certain clinical characteristics also played a role in the efficacy of topical voriconazole. Nonresponders to voriconazole were more likely to have peripheral infiltrates (38.5 % vs. 7.7 %, $P = 0.16$) and hypopyon (61.5 % vs. 23 %, $P = 0.11$) as compared with responders. [44]

To compare safety, efficacy and cost-effectiveness of voriconazole with natamycin, a double-blinded RCT was conducted in two hospitals in India in 2010. This study found no significant difference between the two agents.[23] Natamycin is commercially available, and there is more experience with using it. Topical voriconazole is not commercially available; however it has a wider antifungal coverage. Voriconazole may be the first choice in patients who have a higher risk for *Candida* keratitis but also requires having a good antifungal coverage against other species. It is therefore, unclear whether or not voriconazole should supersede natamycin as a first line treatment for fungal keratitis.

Econazole

It was theorized that use of both natamycin and econazole in the management of fungal keratitis may result in a more rapid resolution of corneal ulcers, especially since the mechanisms of action are different. A RCT compared the result of 47 patients with concurrent use of 5 % natamycin and 2 % econazole with a historical control and showed that there was no significant difference (P=0.9) between the two arms for success, which was defined clinically.[45]

Fluconazole

Fluconazole is a synthetic bistriazole available in oral, topical, and IV preparations. It is shown to have a low side effect profile, good intraocular penetration, and a worthy agent to use in *Candida* keratitis with deep lesions.[46] Fluconazole has also been found efficacious in patients who do not respond to natamycin or miconazole in the treatment in the treatment of *Candida* keratitis. Topical 2 % fluconazole was found to be efficacious in six Indian patients with microscopy and culture-proven *Candida* keratitis with deep lesions. Three of these patients had not responded to topical natamycin, while the other three had not responded to topical miconazole.[46] Yet we must be cautious when we interpret this data, as natamycin is known to have poor coverage against *Candida* species.

A limitation of fluconazole is its narrow coverage of filamentous organisms. A prospective evaluation of the comparative safety and efficacy of topical natamycin and 0.2 % fluconazole in eight patients with filamentous fungal keratitis was terminated because of poor response to primary treatment with topical fluconazole. The authors concluded that fluconazole could not be considered as an agent if choice in the therapy of keratitis caused by filamentous fungi.[47] However, there is increasing evidence that shows the efficacy of subconjunctival fluconazole as an adjunct to topical amphotericin B to presumably broaden coverage in the treatment of keratomycosis.[48] A retrospective case series also showed that fluconazole can be resourceful in the treatment of filamentous fungal keratitis that was confined only to the superficial layers of the cornea.[49]

Ketoconazole

Ketoconazole is available in an oral and topical form. It is known to have good in vitro activity against *Aspergillus*, *Candida*, and *Curvularia* species; however, there are variable results obtained when treating keratitis despite its excellent concentration in the anterior chamber of the eye when administered by oral route. Concomitant administration of oral ketoconazole and topical miconazole was reported to be efficacious for clinical mycotic keratitis.[50]

Expert Discussion

Many retrospective case series in different parts of the world at different times have shown that a significant portion of patients still require aggressive, surgical intervention after failed medical treatment.[29,51,52] In these randomized controlled trials, there was no significant difference in the outcome using either natamycin, voriconazole, or econazole although the frequency of filamentous fungi species was different (for example frequency of *Fusarium* was 35 %–38 % in one study and 54 %–60 % in the other). A Cochrane systematic review could not conclude that any antifungal medication was superior to the other. In addition, retrospective studies show that the type of medications used did not seem to influence the need for surgical intervention.[35] Furthermore, combination of antifungal therapy seems to be not superior to single therapy.[45,53,54] In a retrospective case series, 358 patients were hospitalized and treated with topical 1 % fluconazole combined with 0.25 % amphotericin B or 5 % natamycin drops every hour, alternating on the half hour. All patients were also treated with oral fluconazole. An antifungal ointment was applied to the scraped lesions during sleep. Some patients with hypopyon were given 100 mg fluconazole intravenously twice a day. However, 30 % of the patients still required surgical intervention.[55] In contrast, in a case series, 16 % (2/12) patients who were treated with intrastromal voriconazole required surgical intervention.[56] In two other different case series, overall six patients were treated with intrastromal voriconazole and again 16 % (1 /6) did not respond to treatment.[57,58] Although it is difficult to compare the reported treatment failure in these RCTs (11 %–18 %) with other retrospective case series (23 %–36 %) and intrastromal injection of voriconazole (16 %), these results suggest that the outcome of medical treatment may be not directly related to whether a single or a combination of antifungal therapy is used, or whether it is given topically or systemically. What seems to be more important is to ensure that the concentration of the medication is always maintained above the MIC90 of the fungus; as it is presumably achieved in these RCTs by giving the medication in the hospital though intrastromal injection of voriconazole.

One can conclude that adherence of patients to treatment is also an important factor that influences the outcome, especially when the majority of fungal keratitis patients are working-class young males who must instil natamycin eye drops into an inflamed eye every hour during the day and every two hours during the night. This is also compounded by availability of the medication, and its ease of use and side effect profile. Most importantly, cost of medication and access to care are likely the most prominent barrier to treatment of fungal keratitis in lower socioeconomic populations. Given the high risk of ocular morbidity because of FK, patients need to have a clear understanding of the duration of treatment and the likelihood of response.

Surgical treatment

Surgical intervention is currently an option for patients with disease that is refractory to medical treatment to control deep and severe fungal infections. It is usually done within 4 weeks of presentation in order to limit progression of the infection to other areas of the eye which portends a poorer prognosis.[19] Corneal scraping as a surgical treatment for fungal

keratitis has been recommended previously because it was thought that by removing the superficial epithelial layers, thereby increasing the penetration of antifungal medication[59] and removing fungal elements from the superficial layers of the cornea, the outcome would be better. However, a recent well-designed randomized control trial (RCT) suggested that continued corneal scraping may worsen BSCVA (best correct visual acuity) at 3 months in patients treated with either natamycin or voriconazole (p=0.06) and suggested that corneal scraping should be limited to obtaining samples.[23]

Penetrating Keratoplasty

The most common surgical intervention (other than corneal scraping) is penetrating keratoplasty (PK). PK is a procedure in which trephines are used to excise lesions of the cornea and a donor corneal graft is sutured in place. Previous studies have shown PK as an effective option for treatment of refractory or severe cases of fungal keratitis.[55,58] PK has also been shown as an effective way to treat fungal corneal perforations. In a retrospective review, 52 eyes with corneal perforations secondary to FK were followed after PKs. Forty-four grafts (84.6 %) remained clear at final follow-up, and 46 eyes (88.5 %) had improved visual acuity. [60] The most common complications of PK are graft rejection, recurrence of fungal infection, graft ulcers, and secondary glaucoma. Graft rejection is particularly high in PK secondary to keratitis because of secondary infection or inflammation of the newly grafted tissue.

In order to delay or prevent PK, tissue adhesive has been used in patients with severe thinning of the cornea or impending perforation.[61] Amniotic membrane transplantation (AMT) has emerged as a stopgap measure to prevent PK secondary to fungal keratitis. Amniotic membranes have been used to facilitate ocular surface reconstructions in other ocular surface conditions. Through AMT, active components in the membrane such as nerve growth factors are thought to reduce pain while supporting re-epithelialization of tissue.[62] In one study, amniotic membrane transplantation was used in 23 culture-proven, acute fungal keratitis patients with non-healing corneal ulcers, or impending cornea perforation to prevent PK or to promote re-epithelialization. Following transplant, 25 % of patients with persistent positive culture for fungus required PK. The final visual outcome was BCVA > 20/400. It improved in 17, did not changed in 4 and worsened in 2 patients.[63]

One reason to delay PK is that in an inflamed eye is because infection may be introduced into the anterior chamber or vitreous. Another reason to delay PK is that corticosteroids, which are usually used to prevent cornea graft rejection, may increase the chance of recurrence of fungal infection. Following PK, oral and topical antifungal medications are usually continued for 2 weeks and if pathology reports presence of fungus on the margin of the cornea sample, treatment continues for 6–8 weeks. The patient is vigilantly followed up for the signs of recurrence or graft rejection.

Cyclosporine has been recommended after PK in the setting of fungal keratitis because it has been suggested to have dual antifungal and anti-immune properties.[64] However; direct evidence to support this notion is limited to a case report of three patients who had PK following fungal keratitis. Further studies are required to evaluate the risk and benefit of steroid and cyclosporine in the management of fungal keratitis patients undergoing corneal transplant.

Lamellar Keratoplasty

There is emerging evidence that an alternate surgical procedure, lamellar keratoplasty (LK) may change the current surgical management approach to fungal keratitis. Selective LK is a procedure in which only diseased layers of the corneal surface are excised, retaining the

underlying basement structures of the cornea intact. The rationale for selecting LK over PK is when fungal invasion is focal and only transplantation of the diseased layer is needed instead of the entire cornea. It has also been suggested that selective LK retains the normal architecture of the corneal surface, allowing for a more stable corneal surface and tectonically stronger eye than PK. [65] It has also been proposed that by leaving the host endothelium and Descemet's membrane intact, the risk of endothelial rejection, the most severe type of corneal graft rejection, can be eliminated.[66] In one center in Shandong, China, the leading indication for lamellar keratoplasty (LK) in 2008 was infectious keratitis, and the subcategory of fungal keratitis cases constituted 67 % of the infectious keratitis cases.[67] 55 antifungal refractory patients underwent LK with intensive topical and oral antifungal medication. Cases were diagnosed based on cornea scrapings or confocal microscopy. They reported that in 93 % of the patients, the fungal infection was eradicated. The remaining four patients were treated by a secondary PK. Visual acuity ranged from 20/20 to 20/63 with a few complications after 6–18 months follow-up. [68] Following this report, they published another paper, showing that surgical intervention was performed in 92 % of fungal keratitis cases. PK was performed in 66 % of cases and LK was performed in 29 % of cases (n=177). They reported that they saved the integrity of the globe in 96 % of the cases. They concluded that early surgical intervention, especially LK, should be considered as treatment of choice for severe fungal keratitis if aggressive antifungal treatment fails. [69] They added that the chance of recurrence of fungal infection following LK is the highest within the first week of surgery and preoperative immunosuppressive or corticosteroid therapy increases the risk of recurrence.[70]

In another retrospective case series, investigators compared the outcomes of deep anterior lamellar keratoplasty (DALK) (n=26) with PKP (n=100) in patients with severe fungal, bacterial or *Acanthamoeba* keratitis. There was no significant difference between the two groups in terms of eradication of infection (84 % vs. 86 %, p=0.74). However in DALK group, 50 % achieved BCVA > 6/9 while in PKP group, 20 % had the same visual acuity (p=0.01). In the DALK group, 12 patients experienced recurrence of infection and 6 of them developed endophthalmitis with poor outcome. Kaplan–Meier survival analysis at 1 year also showed that in DALK group, the chance of graft survival was better than PKP group (90 % vs. 78 %).[71] These results suggest that LK and DALK may be considered earlier if the patient has been pre-treated intensively with antifungal medications and before letting the infection to progress into deeper layers of the cornea.

Conclusion

Fungal keratitis, though seemingly straightforward, is a complex entity with many considerations when it comes to diagnosis and treatment. It is particularly a public health concern in developing countries where limited access to care and economic barriers can cause visual loss in a demographic that is primarily young. As with all corneal infections, proper identification of microbe and targeted therapy can mitigate complications. In fungal keratitis, it is important to note that clinical suspicion, particularly in areas in which the disease is endemic, is paramount to the diagnosis. Gram staining and KOH wet mounts can be early, sensitive measures used to differentiate a fungal agent versus a bacterial cause. They may also provide a clue as to what pharmacological therapy can be most effective. Though culture remains a necessary step in diagnosis, time is a limiting factor and treatment should not be delayed. Newer modalities such as PCR and confocal microscopy are effective but are prohibitively expensive and are not readily utilized in all facilities. Antifungal therapy choices are vast and the literature on each specific therapy is rich. Though topical natamycin is the first-line therapy for superficial mycosis, oral therapy should be considered if the infection is more advanced. PK and LK are effective surgical options in medically refractory cases.

Acknowledgments

NIH Center Core Grant P30EY014801, RPB Unrestricted Award and Career Development Awards Dr. Galor, Department of Defense (DOD- Grant#W81XWH-09-1-0675)

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• Of importance

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Table 1-1

Agents implicated in fungal keratitis

Center	Most Common	Second Most Common
Bangkok, Thailand 30[12]	*Fusarium*	
Bascom Palmer Eye Institute, Florida [19]	*Fusarium*	
Shandong, China[72]	*Fusarium*	*Aspergillus*
Aravind Eye Hospital, South India[13]	*Fusarium*	*Aspergillus*
Riyadh, Saudi Arabia[73]	*Aspergillus*	*Fusarium*
University of Minnesota, Minneapolis[17]	*Aspergillus* and *Candida*	
Willis Eye Hospital, Philadelphia [40]	*Candida*	*Fusarium*
Melbourne, Australia[74]	*Candida*	*Aspergillus*

Table 1-2

Treatments for fungal keratitis

Category	Mechanism of action	Examples	Comments	Susceptibility
Polyenes	Bind to fungal cell wall ergosterol and disrupts it	Amphotericin B	Poor penetration; toxic to human cells at higher dose; its systemic use with antineoplastic agents or cyclosporine increases the risk of renal toxicity; may cause punctate epithelial erosions and occasionally a greenish discoloration of the cornea.	*Candida* 100 %, *Aspergillus* 50 %, *Fusarium* 50 %
		Natamycin	Less toxic than amphotericin B. No oral form available. Variable *Candida* coverage	*Aspergillus* 100 %, *Fusarium* 100 %
Azoles (imidazoles and triazoles)	At low concentrations inhibit ergosterol synthesis, at higher concentrations appear to cause direct damage to cell walls	Voriconazole	Good cornea penetration and minimum toxicity. Topical as effective as intrastromal.	*Candida* 100 %, *Aspergillus*100 % *Fusarium* 100 %
		Fluconazole	Oral form effective against *Candida* with deep penetration. Narrow coverage against filamentous organisms. Adjust dose for renal insufficiency; monitor for rash, and discontinue if progresses.	*Candida* 100 %
		Itraconazole		*Candida* 100 %, *Aspergillus* 70 %
		Posaconazole	Lowest MIC for *Aspergillus* in an in vitro study.[42] Topical and oral posaconazole shown to effective against resistant ocular fusarium species in case reports.[75,76]	*Aspergillus Fusarium*
		Ketoconazole	Good concentration in anterior chamber by oral route; hepatotoxicity may occur; administer antacid, anticholinergics, or H2 blockers at least 2 hours after taking	*Candida* 100 % *Aspergillus*100 % *Fusarium* 50 % *Culvaria* spp

Category	Mechanism of action	Examples	Comments	Susceptibility
			ketoconazole. Adverse effects including impotence, decreased libido, and gynecomastia.	
Fluorinated pyrimidines	Block fungal thymidine synthesis	Flucytosine	Emergence of resistance rapidly develops if used alone, has synergistic effect with azole or amphotericin B. Narrow efficacy if treating filamentous fungi.	*Candida* 100 %, *Cryptococcus* 100 % *Aspergillus* 20 %
Echinocandins	Block fungal cell wall beta-glucan synthesis	Capsofungin, micafugin, anidulafungin	Controversy over effectiveness in ocular infections.	*Candida* and *Aspergillus*