Clinical Microbiology: Open Access
ISSN: 2327-5073

Anutarapongpan and O'Brien, Clin Microbial 2014, 3:5
DOI: 10.4172/2327-5073.1000168

Research Article Open Access

Update on Management of Fungal Keratitis

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Received date: June 02, 2014, **Accepted date:** September 26, 2014, **Published date:** October 03, 2014

Keywords Perforation; *Fusarium spp*; Keratitis; Ophthalmic

Introduction

Fungal keratitis is one of the major causes of visual loss and blindness [1,2], especially in developing countries, characterized by ulceration, suppuration, destruction of and even perforation of corneal tissues [3]. The most common causative pathogens are *Fusarium spp*, *Aspergillus spp* and *Candida albicans* varying geographically among areas. *Fusarium spp* and *Aspergillus spp* are common in tropical and subtropical eastern countries and southern US [4]. *Candida albicans* is more common in temperate areas such as the northern US [4]. Recent outbreaks of *Fusarium* keratitis associated with multipurpose contact lens solutions have increased the numbers of contact lens associated fungal keratitis. The most common risk factor in many studies is ocular trauma, particularly with vegetative material. Other risk factors include contact lens use, ocular surgery, ocular surface disease, previous use of topical corticosteroids, a compromised immune system, and tropical, humid climates. Fungal keratitis remains a diagnostic challenge and a difficult therapeutic problem for ophthalmic clinicians because these fungal infections of the cornea frequently result in corneal melting, visual impairment and devastating ocular damage if they are not diagnosed early and treated promptly and effectively [5,6]. There is a need for more sensitive and specific diagnostic methods for early detection of fungal keratitis. More effective antifungal agents in terms of antifungal efficacy and corneal tissue penetration are desired for improved clinical outcomes. This review provides an update on management of fungal keratitis.

Diagnosis

Awareness of this condition and developing a clinical suspicion are important keys for early diagnosis. The predisposing risk factors (Table 1), together with the clinical appearance on slit-lamp biomicroscopic examination such as elevated firm slough; hyphate branching ulcers, irregular feathery margins, a dry rough texture, pigmented lesion, and satellite lesions are significant findings suggestive for fungal keratitis [4,7,8]. However in more advanced cases, fungal keratitis may present with an endothelial plaque, hypopyon, ring infiltration, suppurative stromal keratitis, and possible corneal perforation.

To confirm the diagnosis before commencing initial treatment, corneal scraping is indicated, using a sterile blade to scrape along the edges of the ulcerated cornea. The material gathered is placed on clean microscope slides. Staining tests are simple, rapid and inexpensive methods to facilitate diagnosis. For example, a 10% potassium hydroxide (KOH) wet mount, allows direct visualization of the fungal cell wall by partially digesting the proteinaceous components such as host cells and stromal collagen but leaving polysaccharide containing fungal cell walls intact.

Ocular trauma, particularly with vegetative material
Contact lens use
Ocular surgery
Ocular surface disease
Previous use of topical corticosteroid
Compromised immune system (HIV, diabetes)
Tropical and humid climates

Table 1: Risk Factors for Fungal Keratitis

Gram stain is used to identify bacteria and classify them into Gram-negative and Gram-positive groups; it can also be used to identify fungi in 35% to 90% of culture positive cases [9,10]. Sensitivity and specificity of KOH preparation has been reported to range from 62% to 99% and 73% to 99% retrospectively [9,11-13]. Moreover, Giemsa stain and Gomori methenamine silver stain are useful to highlight hyphal fungal fragments. Calcofluor white stain binds to chitin and cellulose in fungal cell wall and demonstrates bright green fluoresces under ultraviolet light. Combined staining either with Giemsa or Calcofluor white stain along with KOH preparation can improve diagnostic accuracy. Culture on multiple selective culture media such as Sabouraud's agar, blood agar, chocolate agar, brain-heart infusion/gentamicin, and thioglycollate broth was required for identification of the causative pathogen as a gold standard diagnosis. In cases epithelium intact, corneal material can be obtained by using a sterile silk suture (6-0 to 8-0) pass through the level of infiltrated cornea and subsequently transfer this suture sterilely onto culture media [14,15].

Corneal biopsy

In culture negative cases demonstrating progressive suspected microbial keratitis despite intensive antimicrobial therapy, corneal biopsies should be considered [16]. Corneal biopsy may have an important role to confirm the diagnosis of fungal keratitis because histopathological evaluation of infected cornea has found that fungi often present deep in the corneal stroma [17]. Culture of the biopsy tissue specimen is practical and may change antimicrobial therapy, resulting in improved clinical outcomes. Multiple surgical techniques have been described, for example; using a sterile blade, microtrephine-assisted, dermatological skin punch of a specified diameter or femtosecond laser-assisted corneal biopsy [14,16,18-20].

Imaging modalities

New technology has provided more rapid real time and noninvasive tools for detection of microbial keratitis, especially fungal keratitis. The confocal microscope, using point illumination and a spatial pinhole to eliminate out-of-focus light, allows *in vivo* examination of the full thickness of cornea [21]. There are many types of confocal microscopes, from first generation to more advanced generation including Tandem scanning confocal microscope (TSCM), slit scanning confocal microscope (SCCM), laser scanning confocal microscope (LSCM). TSCM, no longer commercially available, significantly limits light transmission which produces poor contrast images compared to other confocal microscopes. SCCM such as Confoscan 3 and Confoscan 4 (Nidek Technologies), have a wide slit aperture that allows more light transmission, which improves brightness and contrast of the images and increases depth of field. The Heidelberg retina tomograph rostock corneal module laser scanning confocal microscope (HRT-II/RCM and HRT-III/RCM), using laser light at 670 nm wavelength, provided high-contrast, high-quality images [22]. Many studies showed that it provides high sensitivity and specificity ranging from 88.3-94% and 78-91.1% [23-25], respectively. Although cultures and smears are standard diagnostic methods for fungal keratitis, these microbiology techniques require considerable time and expertise. Definitive identification of causative pathogens is required for start of initial antifungal treatment. This emerging technology may provide rapid and useful diagnosis, especially in the following conditions such as deep stromal infiltrates not accessible to corneal scrapings: long term antifungal therapy while organisms continue to be present in the deep stroma, after intracorneal ring segment implantation, after incisional refractive surgery or LASIK [23]. Moreover IVCM can be used to monitor the response to treatment of fungal keratitis. Limitations of confocal microscope are limited accessibility, cost and quality of images depending highly on the experience of the operating technician.

Molecular diagnostic techniques

Molecular diagnosis with high sensitivity and specificity has attracted more and more attention than the conventional mycological techniques. A variety of molecular techniques based on amplification, such as nested PCR [9,26], real-time PCR [27-29], loop-mediated isothermal amplification [30,31], and nucleic acid hybridization [32]. PCR is an ideal diagnostic method for fungal keratitis because only a small sample material is required to perform the test. Recently, almost all studies targeted the fungal ribosomal DNA regions, such as 18S rRNA, 28S rRNA and internal transcribed spacer regions as amplification targets [26]. Several studies have reported to detect fungal DNA in the corneal sample by PCR-based amplification using universal (panfungal) primers or more specific primers, followed by identification of the fungus by sequencing of the amplified fungal DNA; other studies have reported molecular identification of fungi isolated in culture from corneal scrapings [26]. The advantage is higher detection rates and identification of specific fungal pathogens [33,34] this may lead to the use of PCR as the reference standard for diagnosis of fungal keratitis. However, some investigators mentioned that non-pathogenic microorganisms could be amplified by this technique leading to confusion about the actual diagnosis [35]. The cost of performing the PCR may be more expensive than using conventional microbiological methods and require more specific materials and instrumentation. These methods can possibly be applied for patients in whom conventional tests do not yield positive results. Nest PCR is a very sensitive method but false-positive results are a problem [9,36]. Currently, real-time PCR is the fastest method of the PCR-based techniques [29]; however, the method normally requires a sophisticated instrument and a well-trained medical staff. Nucleic acid hybridization is another molecular method, employing a DNA probe that determines whether a particular organism is present or not. It effectively localizes the DNA and RNA of infectious agents in tissues and no DNA extraction is required [36]. Although this assay is rapid and easy to perform but the sensitivity is lower than other molecular techniques [37,38].

Molecular diagnostic techniques, providing higher sensitivity, greater rapidly were expected to have an important role on the diagnosis of fungal keratitis in the future [32,39].

Treatment

Once diagnosis of fungal keratitis is confirmed, medical treatment should begin immediately. The causative fungal pathogen(s) can be properly identified through laboratory analysis of corneal scraping, vital staining, and microbial culture. Early diagnosis and prompt, effective treatment are important and may prevent loss of vision and blindness for the patient. Fungal keratitis usually requires a prolonged course of treatment with antifungal agent(s) because of the fungistatic activity and poor bioavailability of these agents.

Polyenes

Polyenes bind directly to fungal membrane sterols (especially ergosterol) and create ionic membrane channels, causing osmotic disruption by an increase in membrane permeability. Polyenes also interfere with fungal membrane-associated oxidative enzyme function. Both actions lead to cell death [40-42]. Natamycin, being the only commercially available topical ophthalmic antifungal preparation, has a board-spectrum of activity against filamentous organisms, such as *Fusarium spp*, *Aspergillus spp*, *Curvularia spp*. It is available as a topical 5% suspension and is a first-line therapy for fungal keratitis. Amphotericin B, another polyene, is active aganist yeast and a first-line treatment of keratitis caused by *Candida spp*, commonly administered as a topical 0.15-0.30% solution [43]. Moreover, intracameral, intrastromal, intravitreal, and subconjuctival amphotericin B injection have been reported as adjuvant treatment. These polyene agents are large molecules with high molecular weight and have limited penetration into the deep corneal stromal and the anterior chamber. Intracameral, intrastromal, and subconjuctival amphotericin B injection have not been evaluated extensively. However, a few clinical trials have reported favorable results for treatment of fungal keratitis. Shao Y et al. evaluated the therapeutic effect of intracameral amphotericin B injection compared to 0.15% topical amphotericin B in 60 patients with fungal keratitis. The comparison revealed that intracameral amphotericin B injection leads to faster healing of keratomycosis and reduced time to disappearance of hypopyon [44]. Yoon KC et al. reported that intracameral amphotericin B injection combined with conventional treatment was better than conventional treatment alone in reducing time to disappearance of hypopyon and final improvement [45]. Furthermore, Intracameral amphotericin B has adjuvant effect in cases of fungal keratitis unresponsive to conventional treatment [46]. One case report demonstrated that intrastromal combined with intravitreal amphotericin B injection can successfully eradicate recurrent fungal keratitis with endophthalmitis caused by *Candida glabrata* [47]. The ocular toxicity study showed that Intrastromal injection of

amphotericin B at concentration of less than 10 μg per 0.1 ml was safe in the rabbit corneas [48]. Subconjuctival amphotericin B therapy has also been reported in a small case series as an adjunctive treatment in patients with severe fungal keratitis but subconjunctival nodules and necrosis are possible adverse effects [49,50].

Azoles

Azoles primarily target the ergosterol biosynthesis pathway by inhibition of cytochrome P450 (CYP)-dependent C-14α demethylase converted lanosterol to ergosterol, an essential component of the fungal cell wall [40]. Certain triazoles, for example; fluconazole, itraconazole and voriclonazole, may interact with secondary targets in the ergosterol biosynthesis pathway but an affinity for these secondary targets varies among the agents and pathogen genus [51]. Among species the triazoles varies in their primary target (14α demethylase) and secondarily targets inhibition in the ergosterol biosynthesis pathway, which may cause the differences in antifungal activity in this class. Azoles are classified into 2 groups, imidazoles including econazole, miconazole, and ketoconazole; triazoles including fluconazole, itraconazole, voriconazole, and posaconazole. Ketoclonazole is the first successful orally absorbable broad-spectum antifungal azole, currently used as an oral pill and 1-2% ketoclonazole suspension topical form in treatment of patients with fungal keratitis [51-54]. 1% Miconazole and subconjuctival miconazole (10 mg/0.5 ml) have been reported in 2 case series as the treatment for fungal keratitis cause by filamentous fungi and *Candida* [55,56]. 2% econazole was found to be as effective as 5% natamycin in a randomized controlled trial in 112 fungal keratitis patients but combined both of them have not gain more benefit [57,58]. Itraconazole is given by oral (200-400 mg/day) or 1% suspension topical form in therapy of ophthalmic mycoses [59-61]. Subconjunctival or topical fluconazole adding to topical natamycin showed positive results in treating severe fungal keratitis [62,63]. Subconjuctival fluconazole in combination with topical amphotericin B has been reported to provide better outcomes as well [64,65]. Otherwise, topical fluconazole alone should be used with caution because an extremely poor clinical response with monotherapy in one randomized clinia trial for fungal keratitis [66-68]. Voriconazole, a new generation triazole antifungal agent, possesses a very broad spectrum of activity against dermatophytes, yeast, and molds. Many studies showed adequate aqueous and vitreous concentration after topical and oral voriconazole treatment for various fungal pathogens [69,70]. A large study assessing filamentous fungal susceptibility using ocular isolates from 221 keratitis cases in south India disclosed overall that organisms had lower MICs to voriconazole than to natamycin, but Fusarium isolates were less susceptible to voriconazole and *Aspergillus flavus* isolates appeared to have lower susceptibility to natamycin compared to other organisms [71]. Moreover, a number of case series showed promise for delivering successful management of mild to severe fungal keratitis with topical, intrastromal, and oral voriconazole [72-75]. In contrast, several randomized clinical trials did not find a significant difference in treatment outcomes between voriconazole and natamycin [76-78]. A large randomized double-masked control trial called The Mycotic Ulcer Treatment Trial (MUTT) enrolled 368 patients to compare topical voriconazole 1% versus topical natamycin in the treatment of filamentous fungal keratitis. This study found that topical natamycin is superior to topical voriconazole and voriconazole monotherapy is not recommend for filamentous fungal keratitis [79]. Sharma N et al. found that topical voriconazole could potentially add benefit to topical natamycin in recalcitrant fungal keratitis [80]. Ramakrishnan et al. reported a 50% successful treatment rate in combining topical, oral, and/or intracameral, intrastromal voriconazole with natamycin [81,82]. Posaconazole is another new triazole agent. Topical and oral posaconazole have been used in therapy of fungal keratitis, with one case series reporting successful treatment of Fusarium keratitis, resistant to voriconazole [83,84].

Echinocandins

Echinocandins, synthetic lipopeptides, are derived from fermentation products from several different fungi. These agents disrupt cell wall synthesis by inhibiting β1,3-D-glucan synthase and possess a narrow antifungal spectrum that is restricted to *Candida spp* and some *Aspergillus spp*. Echinocandins, include caspofungin, micafungin, and anidulafungin. Recently, one case reported by Hurtado-Sarrio et al. demonstrated successful treatment of *Candida albican* keratitis refractory to voriconazole using topical caspofungin [85]. Tu EY reported 3 cases of *Alternaria* keratitis refractory to voriconazole and natamycin and successful treatment by topical caspofungin and topical fluconazole [86,87].

Allylamines

Allylamines interfere with the ergosterol synthesis pathway by reversibly inhibiting squalene epoxidase enzyme. Terbinafine, only one agent in this group, demonstrates excellent *in vitro* fungicidal activity against many dermatophytes but poor activity against many yeasts (Tables 2 and 3). A retrospective case series of 90 filametous keratitis patients found that topical terbinafine was as effective as topical natamycin but may take longer treatment duration [88].

Study design	Intervention	Number of patients	Causative organisms	Outcomes criteria	Conclusion
Prospective controlled clinical trial Shao Y et al. [44]	Intracameral Amphotericin B (10 μg/0.1 ml) vs Topical Amphotericin B 0.15%	60	Not revealed	Clinical response by healing of the ulcer	Intracameral Amphotericin B superior to topical Amphotericin B
Clinical trial Yoon KC et al. [45]	Intracameral Amphotericin B (10 μg/0.1 ml) + conventional treatment vs conventional treatment (Topical Amphotericin B 0.15% +Topical Fluconazole 1% + Oral Fluconazole 200 mg/day)	31	10 *Fusarium spp* 7 *Aspergillus spp* 6 *Candida spp* 3 *Alternaria spp* 1 *Curvularia spp* 4 Unidentified	Clinical response by healing of the ulcer (time to disappearance: hypopyon, epithelial defect closure, final improvement)	Intracameral Amphotericin B and conventional treatment superior to conventional treatment

Case series Yilmaz S et al. [46]	Add intracameral Amphotericin B (5 µg/0.1 ml)in cases that did not response to conventional treatment (Topical Fluconazole 0.3%, intravenous Fluconazole + Oral Itraconazole)	14 eyes in 12 pt	2 *Fusarium spp* 4 *Aspergillus spp* 6 *Candida spp* 2 unidentifed hyphae	Clinical response by healing of the ulcer	Intracameral Amphotericin B adjuvant effect in case unresponsive to conventional treatment
RCT Prajna et al. [57]	Topical Econazole 2% vs Topical Natamycin 5%	112	64 *Fusarium spp* 30 *Aspergillus spp* 6 *Curvularia spp* 2 *Cladosporium* 10 unidentifed hyphae	Clinical response by healing of the ulcer	No difference
Clinical trial Kalavathy Cm et al. [61]	Topical Itraconazole 1% vs Topical Natamycin 5%	100	42 *Fusarium spp* 21 *Aspergillus spp* 11 *Curvularia spp* 14 other fungi 12 unidentifed hyphae	Clinical response by healing of the ulcer	Overall no difference but Natamycin superior in *Fusarium*
Clinical trial Mahdy RA et al. [64]	Topical Amphotericin B 0.05% + Subconjuctival Fluconazole (1 mg/0.5 ml) vs Topical Amphotericin B 0.05% alone	48	4 *Penicillium spp* 20 *Aspergillus spp* 14 *Candida spp* 10 unidentifed	Clinical response by healing of the ulcer	Combine therapy superior to monotherapy
RCT Prajna NV et al. [76]	Topical 1% Voriconazole vs Topical 5% Natamycin	120	44 *Fusarium spp* 19 *Aspergillus spp* 39 Other filamentous fungi	1st BCVA 2nd scar size, perforation	No significant differences in visual acuity, scar size and perforations between the two groups
Clinical trial Arora R et al. [77]	Topical 1% Voriconazole vs Topical 5% Natamycin	30	13 *Aspergillus spp* 12 *Curvularia spp* 5 Other filamentous fungi	Clinical response by healing of the ulcer	No difference
Retrospective review Ramakrishnan T et al. [81]	Topical 1% Voriconazole, Oral voriconazole (400 mg), Topical 5% Natamycin, Intrastromal Voriconazole, Intracameral Voriconazole	26	7 *Fusarium spp* 3 *Aspergillus spp* 4 *Candida spp* 3 *Scedosporium Spp* 9 other fungi	Clinical response by healing of the ulcer	Successful management in 50% of cases
RCT Parchand S et al. [78]	Gr1:Topical 1% Voriconazole + Oral voriconazole (400 mg) Gr2: Topical 5% Natamycin+ Oral voriconazole (400 mg) Gr3: Topical 5% Natamycin+ Oral itraconazole (400 mg)	45	6 *Fusarium spp* 8 *Aspergillus spp* 2 *Curvularia spp* 1 *Acremonium Spp* 28 unidentifed	1st Clinical response by healing of the ulcer 2nd Corneal opacity, BCVA	No difference
RCT Prajna NV et al. [79]	Topical 1% Voriconazole vs Topical 5% Natamycin	368	128 *Fusarium spp* 54 *Aspergillus spp* 141 Other filamentous fungi	1st BCVA 2nd perforation and/or PKP	Topical natamycin superior to topical voriconazole
RCT Sharma N et al. [80]	Topical 1% Voriconazole +Topical 5% Natamycin vs Intrastromal Voriconazole +Topical 5% Natamycin	40	7 *Fusarium spp* 12 *Aspergillus spp* 5 *Curvularia spp* 1 *Alternaria* 15 No growth	1st BSCVA 2nd time to healing and the size of the scar	Topical Voriconazole seem to be useful adjunct to Natamycin

Table 2: Clinical trials for treatment of fungal keratitis showing results of different antifungal medications.

	Generic name	Ophthalmic drug	Periocular and Intraocular Injection	Systemic drug
Polyenes	Natamycin	5% Natamycin		
	Amphotericin B	0.15% Amphotericin B [44,45]	Subconjuctival injection: 0.3 ml Amphotericin B (5 mg/ml) [49]	
		0.3% Amphotericin B		
		0.5% Amphotericin B	Intracameral injection: 10 µg Amphotericin B (100 µg/1 ml) [44, 45]	
		0.05% Amphotericin B63	5 µg Amphotericin B (50 µg/1 ml) [46]	
			Intrastromal injection: 0.05 ml Amphotericin B (5 µg/0.1 ml) [47]	
			Intravitreous injection: 5 µg Amphotericin B (50 µg/1 ml) [47]	
Azoles	Imidazole:			
	Econazole	2% Econazole [57, 58]		
	Miconazole	1% Miconazole [55, 56]		
	Ketoclonazole	1-2% Ketoclonazole [52, 54]		Ketoclonazole by oral (200-400 mg/day) [53]
	Triazole:			
	Fluconazole	0.2-0.3% Fluconazole [46, 67]	Subconjuctival injection: Fluconazole 0.5 ml (2 mg/ml) [67]	Fluconazole(50-100 mg /day) [66, 68]
		1% Fluconazole [45]	Fluconazole 0.5 ml (20 mg/ml) [62]	Itraconazole by oral (200-400 mg/day) [59, 60]
	Itraconazole	1% Itraconazole [59]		Voriconazole by oral (400-800 mg/day) [78, 81]
				Posaconazole (800 mg/day) [83, 84]
	Voriconazole	1% Voriconazole [79]	Intrastromal injection: 50 µg Voriconazole in 0.1 ml (0.5 mg/ml) [80]	
			Intracameral injection: 100 µg Voriconazole in 0.1 ml (1 mg/ml) [82]	
	Posaconazole	10% Posaconazole [84]		
Echinocandins	Caspofungin	0.5%Caspofungin [85, 86]	Intrastromal injection [87]	
	Micafungin			
Allylamines	Terbinafine	0.25%Terbinafine [88]		

Table 3: Summery of Antifungal therapy in Fungal keratitis.

Corneal collagen cross linking

Corneal collagen cross linking is an exciting new technique using the photosensitizer riboflavin (vitamin B2) and ultraviolet A (UVA) irradiation at 370 nm to induce increasing corneal tissue strength and rigidity [89]. Originally, this intervention was introduced for treatment of corneal ectasias such as keratoconus. The effects of UV irradiation onto riboflavin saturated cornea generates oxygen and superoxide anion radicals [90] that induce intra and/or interhelical collagen cross-links, These activated radicals could inactivate microbial pathogens [91]. Several studies demonstrated *in vitro* antimicrobial activity of corneal collagen cross linking against varies pathogens [92-96]. Anwar et al. first reported successful treatment of *Aspergillus* keratitis with UVA-riboflavin CXL, along with antifungal

treatment in human eye [97]. Saglik et al. reported Riboflavin/UVA treatment to be useful as a coadjuvant to topical voriconazole in fungal keratitis [98]. Zhiwei Li et al. reported 6 cases of fungal keratitis (*Aspergillus spp*, *Fusarium spp*) successfully treated with Riboflavin/UVA and antimicrobial therapy [99]. Riboflavin/UVA adjuvant to antimicrobial therapy seems to be a promising technique for management of fungal keratitis. Further randomized clinical trials are required to establish the risks and benefits of CXL.

Corneal debridement

Most antifungal agents have poor bioavailability and limited penetration into deeper layers of the cornea, especially in cases of fungal keratitis with intact corneal epithelium. Serial debridements of corneal epithelium seem to be useful to increase drug penetration. A recent survey revealed that ophthalmologists rescrape during the treatment course of fungal keratitis with natamycin more than with voriconazole [87]. In contrast, one randomized double-masked control trial included 120 patients randomized to receive either topical natamycin or topical voriconazole and either had repeated scraping of the epithelium or not. This comparison failed to demonstrate a benefit to this intervention but showed worse outcomes in the scraping group [76].

Surgical treatment

Despite currently available antifungal drug therapy, severe fungal infections may lead to acute perforation, scleritis, endophthalmitis, and blindness. Surgical treatments try to remove infectious elements and also necrotic tissue and other debris, which may hinder complete healing of the lesion. In cases of descemetocele, corneal perforation, or recalcitrant fungal keratitis not responsive to maximum medication therapy, surgical management should be considered. Which specific surgical procedure depends on severity of disease. Permanent conjunctival flaps [100,101] or amniotic membrane transplantation [102], and use of tissue adhesives [100,103] are some of the other surgical methods used for the treatment of various types of fungal corneal ulcers. Penetrating keratoplasty is major surgical procedure to restore anatomical integrity and eradicate infection, but recurrent fungal infection can occur. Hypopyon, corneal perforation, corneal infection extending to limbus, or lens infection are major risk factors for recurrence of infection [104]. In some cases where infection does not extend through the entire thickness of the cornea, lamellar keratoplasty can be considered [105].

Conclusion

Fungal keratitis is a leading cause of visual loss and blindness worldwide. This condition remains a diagnostic challenge and a difficult management problem for treating ophthalmologists. Awareness of this condition together with knowledge of risk factors is an important key for early diagnosis. As there is often delay or misdiagnosis of fungal keratitis, aggressive diagnostic efforts and maximal therapeutic strategies should be exercised in cases having high suspicion or in failure of keratitis to respond to conventional adequate antibacterial therapy. Progress in research and development of antifungal agents for application to oculomycoses has been slow. Current antifungal agents are limited in their efficacy due to poor solubility, limited penetration and intrinsic toxicities. New areas of research and development into both diagnostic and therapeutic methods may lead to prompt initiation of specific treatment and improved prognosis with better management of the fungal infection.

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