International Journal of Research in Medical and Basic Sciences
Volume 8 Issue 11, Nov 2022 ISSN: 2455-2569 Impact Factor: 7.028
Journal Homepage: http://mbsresearch.com, Email: mbsresearchp@gmail.com
Double-Blind Peer Reviewed Refereed Open Access International Journal

MODERN MANAGEMENT OF FUNGAL KERATITIS: A COMPREHENSIVE REVIEW OF DIAGNOSTICS, DRUGS, AND DILEMMAS

Dr Rakesh Sharma, Senior Resident
Department of Ophthalmology
Regional Institute of Ophthalmology, Government Medical College
Amritsar, Punjab, India

1 Abstract

Fungal keratitis is a severe and an ever-rising ocular infection that is a critical sight-threatening condition that may be found mostly in developing nations in a warm and humid climate. It usually occurs after corneal injuries with organic substance and develops very fast unless it is diagnosed and treated early enough. Fungal cornea infection is associated with less apparent and unpredictable symptoms as compared with bacterial keratitis hence distinguishing the conditions clinically is difficult. In addition, confirmation of the diseased condition at the laboratory level may take much time because of lack of resources or access to modern diagnostic equipment. This leads to poor management on an empirical basis and to poor clinical outcomes. Management of fungal keratitis is complex, as many factors contribute to adverse clinical outcomes; inherently poor corneal penetrating ability of many antifungals, the delay in diagnosis and the emergence of resistance by some fungal species being the most important. Natamycin is the treatment of choice of filamentous fungi, but is slowly being replaced by voriconazole due to increased spectrum and improved penetration into the intraocular space. These, however, do not help effectively in deep stromal infections. Non-responsive or advanced cases require the use of adjunctive treatments e.g. intracameral/intrastromal administration of antifungal fluids, and surgical procedures such as therapeutic keratoplasty. The postprocedural infection leading to graft failure still represents one of the significant clinical challenges, and the paper will offer an exhaustive overview of the available methods of the diagnostic process such as microbiological stains, culture, PCR, and in vivo confocal microscopy, as well as conduct an assessment of the current treatment alternatives in pharmacological and surgical contexts. It also brings to notice the emerging trends in antifungal treatment and drug delivery methods including nanogels and ocular inserts which promise better outcomes. Low-resource only issues such as late presentation, financial pediments, and non-qualified workers are dealt with. The study points out the necessity of early diagnosis, uniform procedures, better access of any diagnostics, and the use of new techniques to minimize the number of fungal keratitis in the world.

Keywords: *fungal keratitis, natamycin, voriconazole, corneal ulcer, antifungal resistance, diagnostics, therapeutic keratoplasty.*

2 Introduction

Fungal keratitis (FK) is a severe eye infection of the cornea which in most cases results in impaired vision or blindness in case of delayed treatment. It is identified to cause 20 to 60 percent of cases of microbial keratitis in the world especially in areas where there is a lot of agricultural activities, hot and humid climates. The fungus mainly causing this condition is filamentous fungi, namely, Fusarium and Aspergillus species, but yeast-like fungi, including Candida, are also implicated, particularly in immunocompromised people. The signs are however, indicative of non-fungal etiologies and result in delays in the diagnosis and treatment in wrong ways. Culture on microbiological bases is still the gold standard in diagnosis but it is time-consuming and laborious. Poor therapeutic response could be linked to the limited power of the conventional diagnostic tools in use, coupled with poor pharmacokinetics of the available antifungal agents. Considering the high burden of FK in low countries and rising antifungal resistance cases, it is time to re-examine the nature of the utilization of the available diagnostic tools and antifungal-related treatment approaches. This article seeks to critically discuss the state using the advantages and shortcomings of FK management especially on new diagnostic methods, drug therapies and obstinate dilemmas in clinical practice.

The fungal keratitis (FK) is one primary health problem in most of the world particularly in developing countries within the tropical and sub tropical regions. It mostly occurs in countries like India, Nepal, Myanmar, Ghana, southern China provinces where the conditions of the environment and workplace exposures present a conducive situation of fungal corneal infections. In such regions, FK represents a significant percentage (varying between 20 to 60 percent) of total microbial keratitis. The incidence is disproportionately high in rural populations, particularly agricultural workers who are often exposed to vegetative matter, soil and the dust particles in the course of their daily routines. The ocular trauma, particularly injuries involving organic substances and plant stems, wooden sticks, crop material and objects contaminated by soil, constitutes the greatest and the most common risk factor of fungal keratitis. Researchers have found out that up to 65 percent of FK cases in endemic areas can be attributed to trauma. The mere touch of abrasions may introduce fungal spores into the corneal stroma and the infection commences. This renders FK especially popular during harvesting seasons when there are maximum concentrations of airborne spores and vegetative debris. Other predisposing factors known to exist other than trauma include long term use of topical corticosteroids that inhibit the immune system by allowing the fungal colonization. Poor hygiene or extended wear of contact lens has been identified as a risk factor, with a fast-growing number of cases being identified as getting in touch with contact lens, especially in developed nations. Cataract extraction or corneal transplants also performed on the eye can undermine cornea integrity and raise vulnerability. There are also systemic factors that predispose a patient to risk such as diabetes mellitus and immunosuppression (whether by HIV or by immunosuppressive medication).

3. Diagnostic Approaches

3.1 (i) Clinical Examination

Slit-lamp biomicroscopy is considered to be the cornerstone in the ocular diagnosis of the suspected fungal keratitis (FK). The characteristic features sought by the clinicians include feathery or rough-edged corneal ulcers, satellite lesions, which surround the main infiltrate, endothelial plaques and

sometimes a hypopyon. Although these results are suggestive of fungal causes, they do not identify FK alone and frequently coincide with bacterial or amoebic keratitis. This may be indicated by the absence of pain, slow movement and dry appearance of the ulcer, which can be a minor indicator but not pathognomonic. In turn, the wrong diagnosis is quite frequent which determines improper antibacterial treatment and the late installation of an antifungal one. Therefore, to complete confirmation, clinical suspects have to be supported through laboratory tests.

3.2 Techniques of Microbiology

Laboratory confirmation of FK is considered by scraping of the cornea, which is gold standard. Samples that are taken off the ulcer margins and base are gram stained, potassium hydroxide (KOH) wet mount and cultured. KOH preparation (that is usually supplemented by calcofluor white staining) permits quick identification of fungal filaments under a fluorescent microscope. It, however, does not show the genus and the species of fungi. Culture on Sabouraud dextrose agar (SDA) will allow accurate species identification but in most cases will take 27 days to grow. Though culture enhances specificity during diagnosis it is labor intensive and usually not exploited in light of unavailability of facilities or trained microbiologists in the rural clinics.

3.3 Molecular approach and imaging methods

Sensitive methods of diagnostics (polymerase chain reaction (PCR)) provide the ability to detect fungal DNA with high sensitivity and speeds in the cases where cultures are negative. But this is also expensive and technical and this limits its use, especially in low income conditions. An in vivo confocal microscope is a non-invasive imaging system capable of real time visualization of fungal hyphae, particularly in the more deep layers of the cornea. This is promising but needs a great level of sophistication so as to be interpreted properly. In the recent past, MALDI-TOF mass spectrometry has been touted as a fast and accurate method of fungal identification, however its applicability in daily clinical methods remains to be studied further.

4. Antifungal Therapies

4.1First-Line Agents

Natamycin 5%, a polyene medicine, is still the main antifungal agent associated with the management of filamentous fungal keratitis. The only topical antifungal approved by the U.S. FDA specifically in ocular applications is natamycin, although it is ideal against Fusarium species, which regularly cause infection by corneal trauma. In spite of a low access to deeper layers of the cornea, numerous studies have demonstrated the higher clinical efficacy of natamycin. It is noteworthy that Mycotic Ulcer Treatment Trial I (MUTT I) revealed that natamycin-treated patients experienced remarkably higher visual acuity and reduced occurrence of corneal perforations than otherwise in patrons treated using voriconazole especially in the case of Fusarium induced keratitis.

Voriconazole 1% is a second generation of triazole antifungals and shows superior penetration into the cornea and the intraocular space compared with natamycin and is particularly active against Aspergillus species and Candida. It has been applied in a topical, oral and an intrastromal injection. Still, a forthcoming study, MUTT II, that looked at oral voriconazole compared with topical therapy, was unable to show a significant benefit either in visual outcomes or in healing ulcers, and questions

have been raised about the systemic toxicity of voriconazole and its cost-effectiveness compared to other agents.

4.2 Unorthodox & Complementary Therapies

When the first-line agents are non-effective or when the pathogen is resistant, other agents are interchanged e.g. amphotericin B (0.15%) used in yeast infection e.g. Candida albicans infection. Other triazole derivatives including itraconazole and posaconazole have been tried with mixed effects in recalcitrant cases. In the case of deep stromal/non-responding ulcers the intrastromal/intracameral injection of antifungal agents offers high local drug concentrations avoiding the drawbacks of topical drug uptake.

Combination therapy in polymicrobial or chronic infections, combination therapy with e.g. natamycin and voriconazole is sometimes used, but no strong evidence exists that this is effective enough to warrant routine use. It should be used with caution because of a possible drug interaction, toxicity, and the absence of agreement in the present treatment guidelines.

5. Clinical Dilemmas, and Surgical Management

Therapeutic keratoplasty (TPK) is required when pharmacology is not able to suppress fungal keratitis (FK) or the infection causes perforation of corneas. Approximately between 15 and 27 percentages of FK causes need surgery. Although a fungal keratitis can be considered a procedure of vision- and globe-saving, the prognosis of graft survival is typically less favorable than that of bacterial keratitis, because it may cause a relapse of infection, host inflammation, and graft rejection. Whether to operate early or later is in dispute: operating early is likely to minimise the risk of perforation and endophthalmitis, but may also be more likely to result in graft failure when the eye is in a state of active inflammation or infection. An amniotic membrane transplantation (AMT) is another adjunct surgery that has been gaining popularity. The technique has proven effective in stimulating epithelial healing, suppressing inflammation and enhancing post-operative outcomes particularly where there is a difficult-to-heal epithelial deformity or limbal stem cell deficiency after keratitis. Clinical dilemma occurs with those cases, when FK appears with bacterial coinfection or sterile inflammation. Use of Topical corticosteroids, which in autoimmune or bacterial keratitis helps in inflammatory control, is inadvisable in fungal infections because it may actually promote fungal growth. However, the mismanagement of the corticosteroids is commonly prescribed in the initial steps as the patients have not been examined by the microbiology examination, resulting in worse conditions and more stromal involvement.

6. Treatment failures and anti fungal Resistance

The development of new antifungal resistance is also of great concern, especially in such species as Fusarium and Aspergillus, which are notorious in their varying patterns of susceptibility. There are multiple reasons why treatment will be unsuccessful, among which delayed diagnosis, interrupted antifungal therapy courses, inadequate empirical therapeutic choices and insufficient access to antifungal susceptibility testing can be listed. Such resistant strains are also selected by monotherapies of overuse or by monotherapies of prolonged use.

Management cannot be simplified by this resistance that hinders the effectiveness of the first line agents such as natamycin and voriconazole, which justify a potential priority of new drugs of an antifungal character. And no less significant is the antifungal stewardship program that enables the rational approach to medication, lack of developing resistance to drugs, and optimal treatment results.

7. Issues Confronting the Resource-limited Settings

Resource-limits In low- and middle-income countries disproportionately affects those countries leading to a significant cause of blindness in those countries that could have been avoided. Nevertheless, the diagnostic facilities, e.g., microbiology laboratories, PCR analysis and so on, are not always available in such areas, and the correct diagnosis is wrong or takes a long period of time. This is further complicated by the fact that the antifungal agents are expensive, and few ones are accessible like voriconazole or amphotericin B.

Patients turn up in case of advanced stages mostly, after having tried some traditional solutions or consulted with inexperienced practitioners. Also, lack of adherence to long term treatment regimes, both economically and educationally, further worsens the situation. These disparities require immediate action to be taken to reduce the impact of FK worldwide with public health measures like community education programs, teleophthalmology outreach, mobile diagnostic unit, and subsidized drug schemes.

8. Research and Management Future Directions

The future of fungal keratitis treatment is in new pharmacotherapy, modern diagnostics, and hospitalized care with the help of technologies. Newer classes of antifungals including luliconazole, isavuconazole, and micafungin are in development to be used in the eye as they have expanded activity and additionally better pharmacokinetics. Meanwhile, drug delivery systems (including nanogels, liposomal formulations, implants, and ocular inserts) are designed to solve the issue of low penetration of drugs into the cornea and increase drug retention time.

Artificial Intelligence (AI) is becoming an effective mechanism in ophthalmology. It is possible that AI-based platforms with slit-lamp imaging and teleophthalmology usage will assist during early triage diagnosis and monitoring of treatment, particularly in rural areas. Thereafter, clinical studies should be conducted at multiple sites to come up with evidence-based guidelines to apply globally considering local microbial patterns, drug resistance pattern, and health systems capacity.

9. Conclusion

Fungal keratitis is an unsolved and a sight-threatening disease, particularly in countries with inadequate access to health care. The diagnostics delays, few treatment alternatives, new resistance, and surgical complications are some of the current weaknesses facing the management arena. Treatment must be more vigorous to overcome treatment resistance and penetrate deep corneal infections, so despite natamycin remaining the standard of medical treatment, new medications and surgical procedures have become necessary.New diagnostic technology, antifungal compositions, and surgical adjuncts promise success, but access and affordability is the limiting factor. Hence, there is

need to incorporate a region-skilled multidisciplinary mode characterized by early, rational drug use, public awareness and technology in order to curb the proportion and sequelae of fungal keratitis world over.

References

Alfonso, E. C. (2011). Diagnosis and management of fungal keratitis. *Clinical Ophthalmology*, 5, 321–327. https://doi.org/10.2147/OPTH.S13002

1. Garg, P., Gopinathan, U., Choudhary, K., Rao, G. N. (2010). Keratomycosis: Clinical and microbiologic experience with dematiaceous fungi. *Ophthalmology*, 117(5), 1001–1008. https://doi.org/10.1016/j.ophtha.2009.10.005
2. Kalavathy, C. M., Parmar, P., Ramakrishnan, R., et al. (2013). Comparison of early keratectomy versus medical therapy in fungal keratitis. *Cornea*, 32(4), 422–426. https://doi.org/10.1097/ICO.0b013e318263d37b
3. Lalitha, P., Prajna, N. V., Kabra, A., et al. (2012). Outcomes in Fusarium, Aspergillus, and other filamentous fungal keratitis infections. *American Journal of Ophthalmology*, 153(5), 853–860. https://doi.org/10.1016/j.ajo.2011.10.017
4. Prajna, N. V., Krishnan, T., Mascarenhas, J., et al. (2013). The Mycotic Ulcer Treatment Trial: A randomized trial comparing natamycin vs voriconazole. *Archives of Ophthalmology*, 131(4), 422–429. https://doi.org/10.1001/jamaophthalmol.2013.85
5. Prajna, N. V., Krishnan, T., Rajaraman, R., et al. (2016). Adjunctive oral voriconazole treatment of fungal keratitis in the Mycotic Ulcer Treatment Trial II: A randomized clinical trial. *JAMA Ophthalmology*, 134(12), 1365–1372. https://doi.org/10.1001/jamaophthalmol.2016.4091
6. Sharma, N., Chacko, J., Velpandian, T., et al. (2015). Comparative evaluation of topical voriconazole and natamycin for fungal keratitis: A randomized controlled trial. *Acta Ophthalmologica*, 93(6), 532–537. https://doi.org/10.1111/aos.12625
7. Thomas, P. A., & Kaliamurthy, J. (2013). Mycotic keratitis: Epidemiology, diagnosis, and management. *Clinical Microbiology and Infection*, 19(3), 210–220. https://doi.org/10.1111/1469-0691.12126
8. Ting, D. S. J., Ho, C. S., Deshmukh, R., et al. (2018). Infectious keratitis: An update on epidemiology, diagnosis and treatment. *Asia-Pacific Journal of Ophthalmology*, 7(6), 415–423. https://doi.org/10.22608/APO.2018413
9. Vemuganti, G. K., Garg, P., & Gopinathan, U. (2009). Fungal keratitis: Diagnosis and treatment update. *Eye & Contact Lens*, 35(4), 190–195. https://doi.org/10.1097/ICL.0b013e3181a97c1c