Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/16390
DOI URL: http://dx.doi.org/10.21474/IJAR01/16390

RESEARCH ARTICLE

FUNGAL KERATITIS - AN UPDATE ON THE GLOBAL THREAT

Dr. Nishat R. Shaikh[1] and Dr. Kashinath G. Choudhary[2]

1. Junior Resident, Department of Ophthalmology, Government Medical College and Hospital, Aurangabad.
2. Head of Department, Department of Ophthalmology, Government Medical College and Hospital, Aurangabad.

Manuscript Info

Manuscript History
Received: 05 January 2023
Final Accepted: 09 February 2023
Published: March 2023

Key words:-
Fungal Keratitis, Microbiology, Fusarium, Aspergillus, Dematiaceous Fungi, Blindness

Abstract

Fungal keratitis (FK) is a sight-threatening disease caused by infection of the cornea by filamentous fungi or yeasts. FK can be challenging to diagnose and treat. In tropical, low, and middle-income countries, it accounts for the majority of cases of microbial keratitis (MK). Filamentous fungi, in particular, Fusarium spp., the aspergilli, and dematiaceous fungi are responsible for the most significant burden of disease. The predominant risk factor for filamentous fungal keratitis is trauma, typically with organic, plant-based material. In 2020, the incidence of FK was estimated to be over 1 million cases per year, with a significant geographical variation. Diagnosing FK is challenging; accurate diagnosis relies on reliable microscopy and culture. Current topical antifungals are not very effective; infections can progress despite prompt treatment. Antifungal drops are often unavailable. When available, natamycin is usually the first-line treatment. However, infections may progress to perforation in ~25% of cases. Future work needs to be directed at addressing these challenges and unmet needs. This review discusses the epidemiology, clinical features, diagnosis, management, and etiology of FK.

Introduction:-

Fungal keratitis, also known as mycotic keratitis, keratomycosis, or oculomycosis, is a severe sight- threatening condition. This highly damaging corneal infection often leads to permanent blindness and eye loss 1,2. The condition is most prevalent in tropical and subtropical locations and has been estimated to account for 20–60% of all culture-positive corneal infections in these climates3. Fungal keratitis tends to be a poorly treated condition with very high morbidity1,2. Corneal infections have been declared a silent epidemic4, yet the size of this epidemic has never been carefully estimated. Fungal keratitis occurs secondary to often minor ocular trauma in most cases. Infected individuals are frequently young, healthy agricultural or outdoor workers who experience an injury from organic matter such as during harvesting2.Traumatizing agents from a variety of plant and animal sources have been recorded, even dust particles2. As men make up a greater proportion of agricultural and outdoor workers, they are more prone to the disease than women. Candida spp infections might superimpose on pre-existing Herpes simplex keratitis or corneal defects from contact lens wearing. Unsafe hygiene practices such as overnight wear and ineffective cleaning have been associated with fungal keratitis. Contact lens wearers of low socioeconomic status are at increased risk of developing the condition, attributed to a inadequate education about hygienic eye care and insufficient cleaning solution use5. Fungal infections of the cornea are caused by more than 100 different species, although over 95% are caused by the filamentous fungi Fusarium spp and Aspergillus spp and the yeast Candida

Corresponding Author:- Dr. Nishat R. Shaikh
Address:- Junior Resident, Department of Ophthalmology, Government Medical College and Hospital, Aurangabad.

spp. Filamentous fungi are responsible for most fungal infections in tropical and subtropical climates, with yeast being more frequent in temperate climates. Corneal infections caused by filamentous fungi tend to have a worse prognosis than those caused by yeast species2. Fungal keratitis typically presents subacutely with eye pain, followed by blurred vision, redness, excessive tearing or discharge, and photophobia. It progresses to ulceration, opacification of the cornea and, more rarely, endophthalmitis6. Corneal perforations are common and five to six times more likely than in bacterial keratitis, and often result in the need for evisceration1. For the patient, the consequences range from visual impairment and blindness, to loss of the globe and disfiguration1.General trends and risk factors are widely reported, but there has been very little epidemiological research conducted in Africa, Asia, and central and South America to calculate its global incidence. The aim of this Review was to appraise the existing literature concerning the incidence of fungal keratitis, the optimal means of making the diagnosis, and to use the most reliable data to estimate the global burden of this condition .

Epidemiology of Fungal Keratitis

Incidence

In 2020, Brown et al. estimated the incidence of fungal keratitis to be 1,051,787 cases per annum, within a range of between 736,251 and 1,367,323 cases per annum[7] The morbidity associated with FK is approximately 10–25% of eyes with FK will perforate or need surgical removal[1,8].

Risk Factors

Despite age and gender not being independent risk factors for fungal keratitis, they both affect other risk factors such as trauma, which is more common in younger men who tend to be agricultural labourers[5,9]. It is also important to note that older patients tend to have a more severe disease and worse outcome[10]. Furthermore, older patients are more likely to have predisposing systemic and ocular co-morbidities such as diabetes mellitus and ocular surface. There have been a number of studies that have suggested an association between HIV infection and fungal keratitis[11]. Other risk factors like traditional eye medicine, topical Corticosteroids, pre-existing ocular surface disease, contact lens usage, prior history of ocular surgery, including cataract, laser-refractive or corneal transplantation surgery[12].

Clinical Features

suggestive of a filamentous fungal infection: firm or dry elevated slough, an irregular or feathery stromal infiltrate edge, satellite infiltrates, an immune ring, and endothelial plaques2. A hypopyon (pus in the anterior chamber) might also be present. Because of the overlap in the clinical signs at presentation, it is often not possible to clinically distinguish fungal keratitis from other types of corneal infection5,13.

Acutely, fungal keratitis typically leads to reduced vision due to the presence of the infection and inflammation in the cornea, blurring the vision 12.

Diagnosis

Conventional microbiological methods remain to be the “gold standard” for the diagnosis of FK. Culture results are highly specific but insensitive and time-consuming, And expertise is required to identify the fungal species isolates precisely2,14,15. Smear microscopy is a rapid and direct method. A recent study shows that the positive detection rate of smear is higher than that of culture15. A suggested set of smears for direct microscopic detection of fungal structures in corneal material would be: a wet preparation (potassium hydroxide or lactophenol cotton blue), a Gram-stained smear, a smear for staining by special fungal stains (Giemsa, periodic acid Schiff, Gomori methenamine silver stain, calcofluor white)2. In vivo confocal microscopy (IVCM) is a rapid method to diagnose FK and is non-inva- sive safe technique, becoming a kind of routine16,17. In addition, it has unique advantages that can monitor therapeutic response16–18. Currently, IVCM is the only means allowing to detect the depth of infection, helping determine the time for appropriate surgical treatment . PCR is a rapid and sensitive diagnostic method, which has been widely used in the diagnosis of in- fectious keratitis19,20.

Ocular Mycology

Fusarium spp.

Fusarium keratitis is a sight-threatening condition that often affects otherwise healthy individuals during their most economically active years of life1,21. Without adequate treatment, infection progresses relentlessly to perforation1,8, endophthalmitis22, and ultimately loss of the eye in the form of enucleation23,24.

Aspergillus sp.
Aspergillus spp. are the second most frequently reported causative organisms of fungal keratitis globally. Several species have been associated with corneal infection, the commonest being A. flavus, A. fumigatus, A. niger and A. terreus13,25,26.

Dematiaceous Fungi
The most commonly reported ocular pathogens after Fusarium spp. and Aspergillus spp. are representatives from the dematiaceous moulds, a diverse group of fungi characterised by their ability to produce melanin, which has long been regarded as a unique pathogenic advantage27.

Curvularia spp. are the most commonly reported of the dematiaceous fungi globally. Many other genera have also been reported to cause keratitis including Bipolaris spp., Exserohilum spp., Alternaria spp., Ulocladium spp., Lasidoplodia theobromae and Colletotrichum spp. 13,19,28.

Other Filamentous Fungi
Other filamentous fungi less frequently reported include: Sarocladium spp, Penicillium spp., Paecilomyces spp., Scedosporium spp. and Purepureocillum lilacinum12.

Management
Anti-fungal treatment
Natamycin, with a broad spectrum and stong anti-fungi activity, is safe and effective at a very low concentration[29]. Currently, natamycin is considered to be the most effective topical medical agent against Fusarium and Aspergillus[30,31]. However, it has poor coverage against Candida species.

Amphotericin B is a drug choice for Aspergillus and Candida, while poor activity against Fusarium species[30]. The side effect of amphotericin B is that it is toxic to human cells at a higher dose. Therefore, it is not a first line drug in treatment of FK while other better agents are at hands[30]. Instrastromal injection of amphotericin B may be an adjunct for deep severe FK. Intracameral amphotericin (ICAMB) can be a safe agent in FK refractory to local conventional therapy to better outcome[32].

Fluconazole is known because of its low side effect and good intraocular penetration[30]. The 0.2% fluconazole is effective in FK combined with 5% natamycin. Subconjunctival injection of fluconazole has been found efficacious in patients unresponsive to conventional antifungal medi- cal treatment of Candida and alternaria keratitis. However, fluconazole has narrow cover- age of filamentous fungi. Oral ketoconazole combined with topical miconazole was effective in FK, but it did not add benefit to topical natamycin in deep FK[30,32].

It has been proposed that liposomal formulation of voriconazole and itraconazole has better antifungal activity and is effective in treatment of FK. Voriconazole aqueous drops have higher penetration and can be used topically in FK[33].

Terbinafine is an efficient anti-fungal agent used in fungal skin diseases. It also inhibits the growth of fungi in cornea. It has been proved that topical terbinafine was effective in filamentous keratomycosis. Tacrolimus (FK506), a novel immunosuppressant, can inhibit the inflammation caused by fungi. Caspofungin eye drops seem to be a possible alternative for treatment of FK. But it still needs more randomized controlled trails.[32]

CXL has been recently used as a promising and worthwhile treatment in refractory infectious ker- atitis, defined as PACK-CXL: photo activated chromophroe for keratitis[32].

Therapeutic Surgical Intervention
Penetrating keratoplasty (PK) is the most commom therapeutic surgery[30]. It has been suggested that early suigical management of PK was require. PK is an effective method in corneal in- fectious and non-infectious diseases resisitant to other treatment[34]. It is critical to remove the infected tissue through surgery to vision. Lamellar keratoplasty (LK) and deep anterior lamellar keratoplasty (DALK) are selected for focal invasion or infection that did not invasive into deep layers of cornea[30].

New Methods

A study used a novel combination of cryotherapy and anti-fungal agents to treat ulcer of FK and found that cryotherapy was effective in treating ulcer. Rose Bengal-mediated photodynamic therapy (PDT) can inhibit the growth of fungi. It may contribute to useful treatment for infectious keratitis. With the role of VDR in innate immunity being discovered gradually, a new target of treatment can be explored for FK. All-trans retinoic acids (ATRA) is proved to have anti-in- flammatory and immunoregulatory effects. However, it is difficult to put the new targets into use clinically. We still need to do more clinical trials[30].

Conclusion:-

Mycotic keratitis, particularly when caused by filamentous fungi, is a global problem. The incidence and main risk factors vary with geographical location and level of economic development; trauma with organic material is the main risk factor whilst in wealthier, temperate countries contact lens use or ocular surface disease are the predominant associations.

References:-

1. Burton MJ, Pithuwa J, Okello E, Afwamba I, Onyango JJ, Oates F, et al. Microbial Keratitis in East Africa: Why are the Outcomes so Poor? Ophthalmic Epidemiology. 2011 Aug;18(4):158–63.
2. Thomas PA. Characteristic clinical features as an aid to the diagnosis of suppurative keratitis caused by filamentous fungi. British Journal of Ophthalmology. 2005 Dec 1;89(12):1554–8.
3. Bongomin F, Gago S, Oladele R, Denning D. Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision. JoF. 2017 Oct 18;3(4):57.
4. Whitcher JP, Srinivasan M, Upadhyay MP. Prevention of Corneal Ulceration in the Developing World: International Ophthalmology Clinics. 2002;42(1):71–7.
5. Deorukhkar S, Katiyar R, Saini S. Epidemiological features and laboratory results of bacterial and fungal keratitis: a five-year study at a rural tertiary-care hospital in western Maharashtra, India. Singapore Med J. 2012 Apr;53(4):264–7.
6. FlorCruz NV, Evans JR. Medical interventions for fungal keratitis. Cochrane Eyes and Vision Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2015 Apr 9 [cited 2023 Mar 4]; Available from:https://doi.wiley.com/10.1002/14651858.CD004241.pub4
7. Brown L, Leck AK, Gichangi M, Burton MJ, Denning DW. The global incidence and diagnosis of fungal keratitis. The Lancet Infectious Diseases. 2021 Mar;21(3):e49–57.
8. Prajna NV, Krishnan T, Rajaraman R, Patel S, Srinivasan M, Das M, et al. Effect of Oral Voriconazole on Fungal Keratitis in the Mycotic Ulcer Treatment Trial II (MUTT II): A Randomized Clinical Trial. JAMA Ophthalmol. 2016 Dec 1;134(12):1365.
9. Bharathi MJ, Ramakrishnan R, Vasu S, Meenakshi R, Shivkumar C, Palaniappan R. Epidemiology of bacterial keratitis in a referral centre in south India. Indian J Med Microbiol. 2003;21(4):239–45.
10. van der Meulen IJ, van Rooij J, Nieuwendaal CP, Cleijnenbreugel HV, Geerards AJ, Remeijer L. Age-related Risk Factors, Culture Outcomes, and Prognosis in Patients Admitted With Infectious Keratitis to Two Dutch Tertiary Referral Centers. Cornea. 2008 Jun;27(5):539–44.
11. Santos C, Parker J, Dawson C, Ostler B. Bilateral Fungal Corneal Ulcers in a Patient With AIDS-Related Complex. American Journal of Ophthalmology. 1986 Jul;102(1):118–9.
12. Hoffman JJ, Burton MJ, Leck A. Mycotic Keratitis—A Global Threat from the Filamentous Fungi. JoF. 2021 Apr 3;7(4):273.
13. Leck AK, Thomas PA, Hagan M, Kaliamurthy J, Ackuaku E, John M, et al. Aetiology of suppurative corneal ulcers in Ghana and south India, and epidemiology of fungal keratitis. British Journal of Ophthalmology. 2002 Nov 1;86(11):1211–5.
14. Lan L, Wang FY, Zeng G. Staining with methylthioninium chloride for the diagnosis of fungal keratitis. Experimental and Therapeutic Medicine. 2013 Nov;6(5):1229–32.
15. Zhao G, Zhai H, Yuan Q, Sun S, Liu T, Xie L. Rapid and sensitive diagnosis of fungal keratitis with direct PCR without template DNA extraction. Clinical Microbiology and Infection. 2014 Oct;20(10):O776–82.
16. Ledbetter EC, Norman ML, Starr JK. In vivo confocal microscopy for the detection of canine fungal keratitis and monitoring of therapeutic response. Vet Ophthalmol. 2016 May;19(3):220–9.
17. van Diepeningen AD, Brankovics B, Iltes J, van der Lee TAJ, Waalwijk C. Diagnosis of Fusarium Infections: Approaches to Identification by the Clinical Mycology Laboratory. Curr Fungal Infect Rep. 2015 Sep;9(3):135–43.

18. Villani E, Baudouin C, Efron N, Hamrah P, Kojima T, Patel SV, et al. In Vivo Confocal Microscopy of the Ocular Surface: From Bench to Bedside. Current Eye Research. 2014 Mar;39(3):213–31.
19. Kumar A, Khurana A, Sharma M, Chauhan L. Causative fungi and treatment outcome of dematiaceous fungal keratitis in North India. Indian J Ophthalmol. 2019;67(7):1048.
20. Burn H, Puri L, Roshan A, Singh SK, Burton MJ. Primary Eye Care in Eastern Nepal. Ophthalmic Epidemiology. 2020 May 3;27(3):165–76.
21. Upadhyay MP. The Bhaktapur eye study: ocular trauma and antibiotic prophylaxis for the prevention of corneal ulceration in Nepal. British Journal of Ophthalmology. 2001 Apr 1;85(4):388–92.
22. Pflugfelder SC, Flynn HW, Zwickey TA, Forster RK, Tsiligianni A, Culbertson WW, et al. Exogenous Fungal Endophthalmitis. Ophthalmology. 1988 Jan;95(1):19–30.
23. Lübke J, Auw-Hädrich C, Meyer-ter-Vehn T, Emrani E, Reinhard T. Fusarienkeratitis mit dramatischem Ausgang. Ophthalmologe. 2017 May;114(5):462–5.
24. Bullock JD, Warwar RE, Elder BL, Khamis HJ. Microbiological Investigations of ReNu Plastic Bottles and the 2004 to 2006 ReNu With MoistureLoc-Related Worldwide Fusarium Keratitis Event. Eye & Contact Lens: Science & Clinical Practice. 2016 May;42(3):147–52.
25. Manikandan P, Abdel-Hadi A, Randhir Babu Singh Y, Revathi R, Anita R, Banawas S, et al. Fungal Keratitis: Epidemiology, Rapid Detection, and Antifungal Susceptibilities of Fusarium and Aspergillus Isolates from Corneal Scrapings. Biomed Res Int. 2019;2019:6395840.
26. Al-Hatmi AMS, Castro MA, de Hoog GS, Badali H, Alvarado VF, Verweij PE, et al. Epidemiology of Aspergillus species causing keratitis in Mexico. Mycoses. 2019 Feb;62(2):144–51.
27. Chongkae S, Nosanchuk JD, Pruksaphon K, Laliam A, Pornsuwan S, Youngchim S. Production of melanin pigments in saprophytic fungi in vitro and during infection. J Basic Microbiol. 2019 Nov;59(11):1092–104.
28. Garg P, Gopinathan U, Choudhary K, Rao GN. Keratomycosis: clinical and microbiologic experience with dematiaceous fungi. Ophthalmology. 2000 Mar;107(3):574–80.
29. Aparicio JF, Barreales EG, Payero TD, Vicente CM, de Pedro A, Santos-Aberturas J. Biotechnological production and application of the antibiotic pimaricin: biosynthesis and its regulation. Appl Microbiol Biotechnol. 2016 Jan;100(1):61–78.
30. Ansari Z, Miller D, Galor A. Current Thoughts in Fungal Keratitis: Diagnosis and Treatment. Curr Fungal Infect Rep. 2013 Sep 1;7(3):209–18.
31. Solanki S, Rathi M, Khanduja S, Dhull C, Sachdeva S, Phogat J. Recent trends: Medical management of infectious keratitis. Oman J Ophthalmol. 2015;8(2):83.
32. Jie wu. Review of clinical and basic approaches of fungal keratitis. Int J Ophthalmol [Internet]. 2016 Nov 18 [cited 2023 Mar 4]; Available from: http://www.ijo.cn/gjyken/ch/reader/view_abstract.aspx?file_no=20161123&flag=1
33. Pahuja P, Kashyap H, Pawar P. Design and Evaluation of HP-β-CD Based Voriconazole Formulations for Ocular Drug Delivery. CDD. 2014 Apr 31;11(2):223–32.
34. Kepez Yildiz B, Hasanreisoglu M, Aktas Z, Aksu G, Kocak BC, Akata F. Fungal keratitis secondary to Scedosporium apiospermum infection and successful treatment with surgical and medical intervention. Int Ophthalmol. 2014 Apr;34(2):305–8.