



Fungal Keratitis

Keratitis refers to inflammation (usually an infection) of the normally transparent cornea of the eye, which causes ulceration and gradual opacification of the cornea, initially due to an influx of inflammatory cells and later, due to fibrosis. Infective (infectious) keratitis may be caused by bacteria, fungi, viruses or protozoa (inflammation without infection may be due to chemical injury) and is the main cause of unilateral corneal scarring^{1,2}. Over 100 different fungi have been described as causes of fungal keratitis and new pathogens are regularly described³. However the common causative agents are *Fusarium* spp., *Aspergillus flavus* and *A. fumigatus* and *Candida albicans* (less common in tropical climates)^{3,4}. In warm, humid climates⁵, approximately 50% of cases of infective keratitis are caused by fungi, but in dry, cool climates, 95% of cases are caused by bacteria.

Corneal abrasion or significant trauma from any type of plant or organic material are the most common predisposing factors⁶. Other risk factors include immunocompromise (including exposure to local or systemic corticosteroids), diabetes, HIV infection⁷, impaired tearing, incomplete eyelid closure and poor hygiene practice in those who use contact lenses. Seasonal variations in incidence have also been described¹.

Incidence

The annual incidence of infective keratitis varies with geographical location.

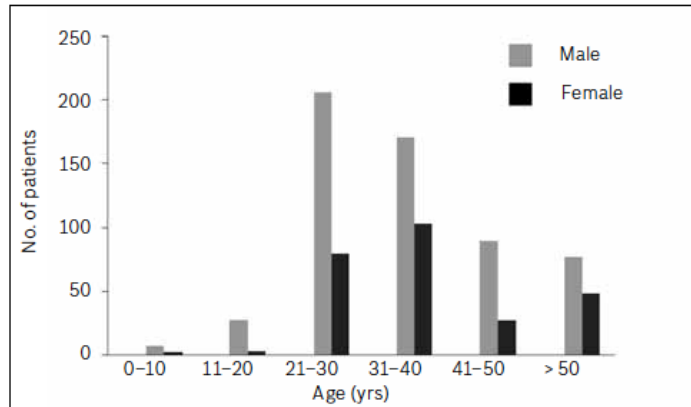
- a. In the USA the incidence is 11 cases x 100,000 inhabitants⁸.
- b. In the UK, the incidence is 0.034 cases per 100,000 per year⁹
- c. In Hong-Kong, 6.3 cases x 100,000¹⁰
- d. In India, 113 cases x 100,000¹¹
- e. In Bhutan, 339 cases x 100,000¹
- f. In Myanmar, 710 cases x 100,000¹
- g. In Nepal, 799 cases x 100,000¹²

It is estimated that 12 million of cases of microbial keratitis occur every year in South East Asia but it is unknown what proportion of cases ends up with visual loss or blindness¹. A statistically significant correlation has been found between Gross National Income (GNI) and aetiology of microbial keratitis. Fungal keratitis is associated with low GNI countries¹³. In 2002, a government report from India estimated that keratitis accounted for 9% of cases of blindness in India¹⁴. In Ugandan children with visual impairment, visual loss after corneal ulceration was responsible for nearly 25% of cases¹⁵.

The annual incidence of microbial keratitis in contact lens wearers varies: 1.2-1,304 /10,000, depending on the type of lens, overnight use and the quality of lens care^{16,17}. The proportion of microbial keratitis cases caused by fungi in contact lens wearers varies from 0.33% to 50%¹³. An international outbreak of *Fusarium*

keratitis in contact lens users occurred in 2004-2006, related to loss of disinfecting capability of the ReNu contact lens solution, now withdrawn¹⁸.

Young adults are predominantly at risk, with men more often affected than women. In one series nearly 4% of cases were found in children¹⁹.



The rate of HIV infection in those presenting with fungal keratitis in Tanzania was twice the documented rate in the adult population⁷, confirmed by other workers¹⁸.

Clinical presentation



The eye exhibits signs of inflammation: injection (redness of the conjunctiva), an anterior chamber reaction and, possibly a hypopyon (pus in the anterior chamber)^{2,3}. Both bacterial and fungal ulcers may present with a large area of central necrosis and a significant hypopyon. Serrated (as opposed to well demarcated) margins, raised slough and colouration other than yellow are statistically more often associated with a

fungal cause, whereas immune ring, keratic precipitates, perineural infiltrates, endothelial plaque, and flare or cells in the anterior chamber are not²⁰ If one of the three distinctive clinical features is present the probability of fungal keratitis is 63%, increasing to 83% if all three features are present²⁰.

Diagnosis

Diagnosis of fungal keratitis is slow and complicated. Confirmation of the diagnosis is made from corneal scrapings or biopsy, by microscopy and culture³. The procedure requires that the eye be anaesthetised with local anaesthetic eye drops. A metal blade is then used to collect material aseptically from the base and margin of the ulcer under direct vision through the magnification of a slit-lamp. The material is then transferred to a clean glass microscope slide, flooded with potassium hydroxide and examined for fungal elements by light microscopy. This method is 60-90% sensitive for hyphae depending on the adequacy of the sample and the interpretive skill of the microscopist. Gram staining is less sensitive, except for identification of *Candida* spp. Other staining methods include Giemsa, lactophenol cotton blue, methanamine silver and calcofluor white; all have strengths and weaknesses³. Biopsy samples may have a slightly higher diagnostic yield.

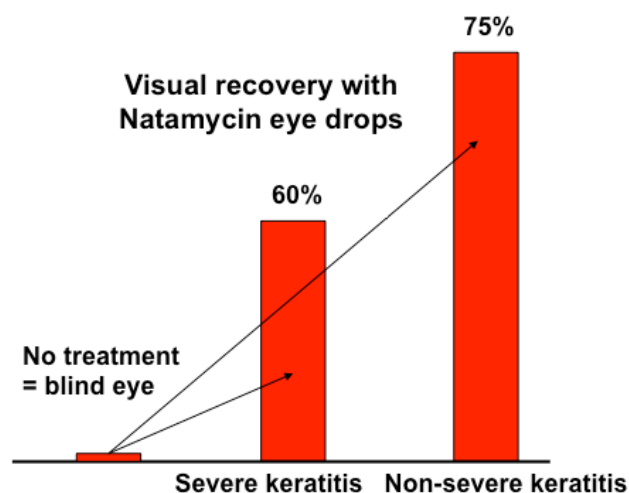
Samples should be cultured on bacterial and fungal media. Fungal growth is typically slow, taking 48 hours to 10 days to become visible. Due to the diversity of fungi cultured from cases of fungal keratitis, examination of cultures by a specialist mycologist is typically necessary to identify the cultures³. *Fusarium* species are the most common, followed by *Aspergillus* spp. and *Candida* spp. Together with *Penicillium* spp., *Alternaria* spp., *Paecilomyces* spp., *Curvularia* spp. and *Bipolaris* spp. these three pathogenic species account for about 90% of cases, with rare fungi (sometimes unidentified) comprising the remainder. Many cultures are negative for bacteria and fungi, sometimes because of prior antimicrobial therapy.

Point of care testing of this disease would dramatically improve patient outcomes.

Treatment

Responses to topical antifungal therapy are reasonable, with 75% of corneas not severely affected and 60% of those severely affected being cured by topical 5% natamycin (Pimaricin)²¹. Other therapies produce similar response rates, although natamycin is superior to voriconazole²². Advanced disease on presentation is associated with worse outcomes.

Natamycin 5% eye drops are registered and available in some countries. The following alternative antifungal eye drops have been used with variable success rates: amphotericin 0.15-0.3%, flucytosine 1%, econazole 1%, miconazole 1%, clotrimazole 1%, itraconazole 1%, fluconazole 1% and voriconazole 1-2%, caspofungin 0.5%³. Oral itraconazole and voriconazole



may be useful in some patients. It is not clear whether intrastromal or subconjunctival antifungal injections contribute to success of treatment of fungal keratitis. Only amphotericin B (IV) and flucytosine (oral) are included in the WHO list of essential medicines. Global availability of natamycin 5% at affordable cost is needed.

Surgery is sometimes required in patients who fail to respond to medical therapy or where there is a threat of ocular perforation or the formation of a descemetocoele. Surgery should be preceded by medical therapy for as long as possible. Surgical procedures include debridement or lamellar keratectomy, formation of a conjunctival flap over a severely ulcerated area of the cornea (in an attempt to save the eyeball), or penetrating keratoplasty if a donor cornea is available. In patients with malignant glaucoma, to restore drainage of aqueous humour, iridectomy, lens excision or anterior vitrectomy may be necessary. In intractable cases, with perforation of the eye, removal of the eyeball (evisceration) is required.

Outcome

A recent report⁷ from Tanzania revealed the poor outcome of microbial keratitis in that geographical area. The study comprised 170 patients. At discharge, 66% were blind in the affected eye, 30% had developed corneal perforation and 8% underwent evisceration, despite antifungal therapy. Late presentation and diagnosis are the principal problems and are a particular feature in resource poor countries with large, (remote), rural, agricultural communities.

Detection of ulceration and prevention

Village health workers can be taught how to diagnose corneal abrasions with strips of fluorescein dye and a blue torch and to start prophylactic antimicrobial therapy if an abrasion is detected^{23,24,25}. Publicity campaigns about the efficacy of prophylactic measures, combined with local health worker training in at risk communities, is effective in reducing the frequency of keratitis.

Opportunities to reduce Global Disease Burden and improve patient outcomes:

A number of feasible initiatives, if widely implemented, could have a very substantial impact on reducing the global fungal keratitis disease burden:

1. Encourage the performance of epidemiological studies including estimation of DALYs to understand the real burden of fungal keratitis,
2. Develop a point care antigen test as a tool for rapid, primary diagnosis,
3. Provide training in classical diagnostic procedures including sampling, culture techniques and fungal species identification,
4. Optimize use of antifungal therapy in resource limited settings through promoting a global approach to the prevention, diagnosis and management of microbial keratitis
 - a. Develop a point of care test that differentiates bacterial infection from fungal infection,
 - b. Investigate the value of introducing combination treatment with antibiotic and antifungal eye drops versus early diagnosis of the cause and targeted therapy,
- b. Ensure that antifungal treatments, especially natamycin eye drops, are readily accessible, especially in rural settings,
- c. Develop prophylactic or pre-emptive treatment guidelines for ocular injuries,
- d. Deliver training in appropriate delivery of the eye drops, dosing and timing,

- e. Encourage the performance of clinical trials to determine the best treatment for fungal keratitis.
 - f. Provide training in classical diagnostic procedures including sampling, culture techniques and fungal species identification.
5. Engage local communities in education and awareness of the benefit of prophylactic measures after eye injury, and provide local healthcare workers with training in detecting corneal abrasion and prophylactic topical antimicrobial medication.

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References

1. Guidelines for the management of corneal ulcer at primary, secondary and tertiary care health facilities in the South-East Asia Region. 2004. WHO Regional Office for South-East Asia. Ophthal/126.
2. Badiee P. Mycotic keratitis. Jundishapur J Microbiol 2013;6:e8561.
3. Thomas PA, Kaliyamurthy J. Mycotic keratitis: epidemiology, diagnosis and management. Clin Microbiol Infect 2013;19:210-20.
4. Leck AK, Thomas PA, Hagan M, et al. Aetiology of suppurative corneal ulcers in Ghana and south India, and epidemiology of fungal keratitis. Br J Ophthalmol 2002;86:1211-5.
5. Whitcher JP. Corneal blindness: a global perspective. Bull WHO 2001;79:214-21.
6. Tilak R, Singh A, Maurya OP, et al. Mycotic keratitis in India: a five-year retrospective study. J Infect Dev Ctries 2010;4:171-4.
7. Burton MJ, Pithuwa J, Okello E, et al. Microbial keratitis in East Africa: why are the outcomes so poor? Ophthalmic Epidemiol 2011;18:158-63.
8. Erie JC, Nevitt MP, Hodge DO, Ballard DJ. Incidence of ulcerative keratitis in a defined population from 1950 through 1988. Arch Ophthalmol 1993, 111: 16-1671.
9. Tuft SJ, Tullo AB. Fungal keratitis in the United Kingdom 2003-2005. Eye (Lond) 2009;23:1308-13.
10. Lam DW, Houang E, Fan DS et al. Incidence and risk factors for microbial keratitis in Hong Kong: comparison with Europe and North America. Eye (Lond) 2002;16:608-18.
11. Gonzales CA, Srinivasan M, Whitcher JP, Smolin G. Incidence of corneal ulceration in Madurai District, South India. Ophthalm Epidemiol 1996, 3: 159-166.

12. Upadhyay MP, Karmacharya PC, Koirala S, et al. Epidemiological characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal. *Am J Ophthalmol* 1991; 111: 92-99.
13. Shah A, Sachdev A, Coggon D, Hossain P. Geographic variations in microbial keratitis: An analysis of the peer-reviewed literature. *Br J Ophthalmol* 2011;95:762-767.
14. Government of India. National survey on blindness. 1991-2001. Report 2002.
15. Waddell K. Childhood blindness and low vision in Uganda. *Eye (Lond)* 1998;12:184-192.
16. Stapleton F, Keay L, Edwards K, Naduvilath T, Dart JK, Brian G, Holden BA. The incidence of contact lens-related microbial keratitis in Australia. *Ophthalmol* 2008;115:1655-62.
17. Jeng BH, Gritz DC, Kumar AB, et al. Epidemiology of ulcerative keratitis in Northern California. *Arch Ophthalmol* 2010;128:1022-8.
18. Ma SK, So K, Chung PH, Tsang HF, Chuang SK. A multi-country outbreak of fungal keratitis associated with a brand of contact lens solution: the Hong Kong experience. *Int J Infect Dis* 2009;13:443-8.
19. 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;53:264-7.
20. Thomas PA, Leck AK, Myatt M. Characteristic clinical features as an aid to the diagnosis of suppurative keratitis caused by filamentous fungi. *Br J Ophthalmol* 2005;89:1554-8.
21. Kalavathy CM, Parmar P, Kalamurthy J, Philip VR, Ramalingam MD, Jesudasan CA, Thomas PA. Comparison of topical itraconazole 1% with topical natamycin 5% for the treatment of filamentous fungal keratitis. *Cornea* 2005;24:449-52.
22. Prajna NV, Krishnan T, Mascarenhas J, et al. The Mycotic Ulcer Treatment Trial: A randomized trial comparing natamycin vs voriconazole. *JAMA Ophthalmol* 2013;131:422-9.
23. Srinivasan M, Upadhyay MP, Priyadarsini B, Mahalakshmi R, Whitcher JP. Corneal ulceration in south-east Asia III: prevention of fungal keratitis at the village level in south India using topical antibiotics. *Br J Ophthalmol* 2006;90:1472-5.
24. Maung N, Thant CC, Srinivasan M, Upadhyay MP, Priyadarsini B, Mahalakshmi R, Whitcher JP. Corneal ulceration in South East Asia. II: a strategy for the prevention of fungal keratitis at the village level in Burma. *Br J Ophthalmol* 2006;90:968-70.
25. Getshen K, Srinivasan M, Upadhyay MP, Priyadarsini B, Mahalakshmi R, Whitcher JP. Corneal ulceration in South East Asia. I: a model for the prevention of bacterial ulcers at the village level in rural Bhutan. *Br J Ophthalmol* 2006;90:276-8.