



## Fungal Keratitis

Keratitis is an infection of the normally transparent cornea of the eye, which causes ulceration and gradual opacification. It may be caused by bacteria or fungi (or chemical injury) and is the main cause of unilateral corneal scarring<sup>1,2</sup>. Over 100 different fungi have caused fungal keratitis and new pathogens are regularly described<sup>3</sup>, however the common causative agents are *Fusarium* spp., *Aspergillus flavus* and *fumigatus* and *Candida albicans*<sup>3,4</sup>. The condition is most prevalent in tropical and subtropical locations. Fungi have been account for 20–60% of all culture-positive corneal infections in these climates (Fig 1). This highly damaging corneal infection often leads to permanent blindness and sometimes eye loss<sup>5</sup>.

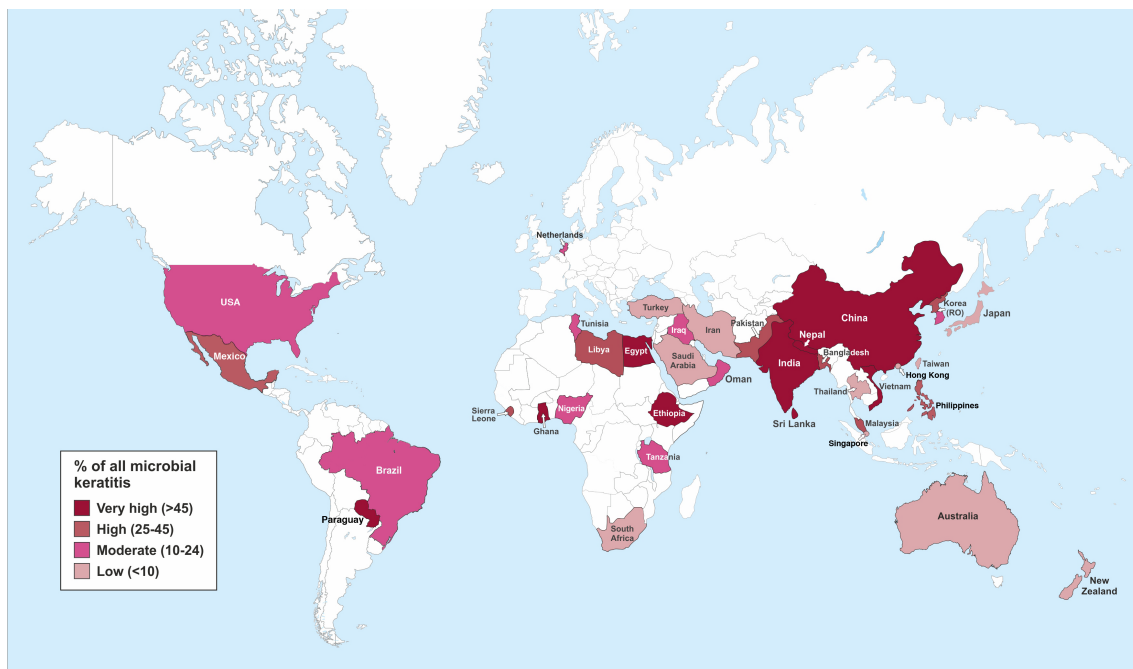


Figure 1. Proportion of microbial keratitis caused by fungi<sup>5</sup>.

Corneal abrasion or significant trauma from any type of plant or organic material are the most common predisposing factors<sup>6</sup>. Other risk factors include immunocompromise (including exposure to local or systemic corticosteroids), diabetes, HIV infection<sup>7</sup>, impaired tearing, incomplete eyelid closure and poor hygiene practice in those who use contact lenses. Seasonal variations in incidence have also been described<sup>1</sup>.

## Incidence

The annual global incidence of fungal keratitis is estimated at 1,051,800 (736,250-1,367,300) cases<sup>5</sup>. The highest estimated incidences are in Asia and Africa, and the lowest in Europe (Fig 2)<sup>5</sup>. This could be an underestimate because some samples are microscopy negative and not cultured for fungi<sup>5</sup>.

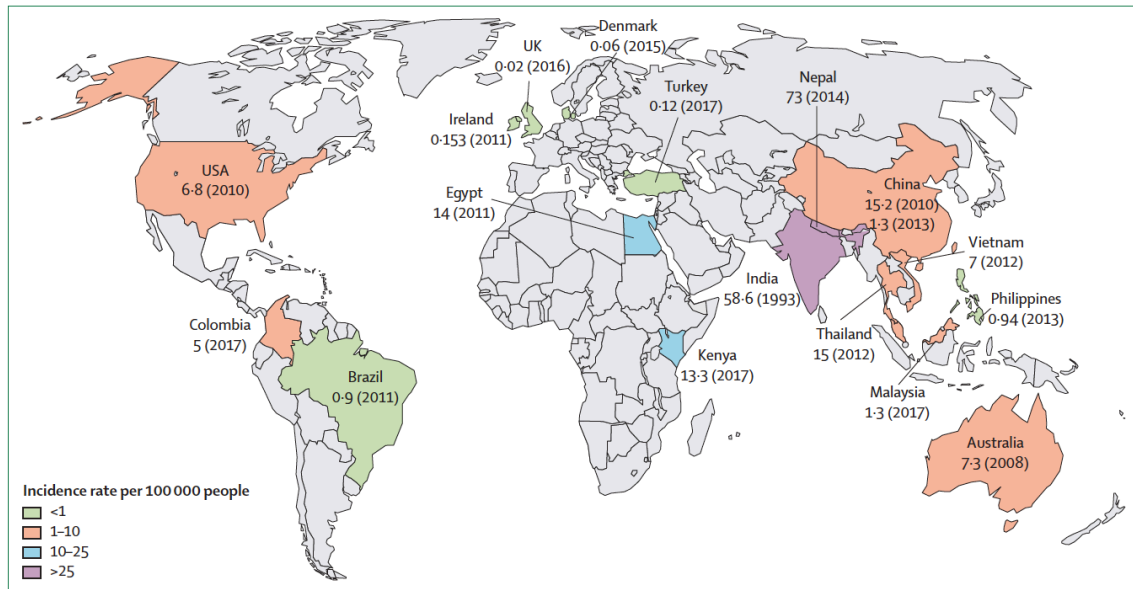


Figure 2. Published annual incidence of fungal keratitis in different countries<sup>5</sup>.

A statistically significant correlation has been found between Gross National Income (GNI) and aetiology of microbial keratitis. Fungal keratitis is associated with low GNI countries<sup>8</sup>. In 2002, a government report from India estimated that keratitis accounted for 9% of cases of blindness in India<sup>9</sup>. In Ugandan children with visual impairment, visual loss after corneal ulceration was responsible for nearly 25% of cases<sup>10</sup>.

Young adults are predominantly at risk, with men more often affected than women. In one series nearly 4% of cases were found in children<sup>11</sup>. The annual incidence of microbial keratitis in contact lens wearers is about 10-fold higher than non-contact lens wearers at 1.2-1,304/10,000, depending on the type of lens, overnight use and the quality of lens care<sup>8,12</sup>. The rate of HIV infection in those presenting with fungal keratitis in Tanzania was twice the documented rate in the adult population<sup>7</sup>, as seen by other workers<sup>13</sup>.

## Clinical presentation



Figure 3. An example of severe *Aspergillus* keratitis

The eye exhibits signs of inflammation: injection, an anterior chamber reaction and, possibly a hypopyon (pus in the anterior chamber)<sup>2,3</sup>. Both bacterial and fungal ulcers may present with a large area of central necrosis (Fig 3) and a

significant hypopyon. Serrated (as opposed to well demarcated) margins,

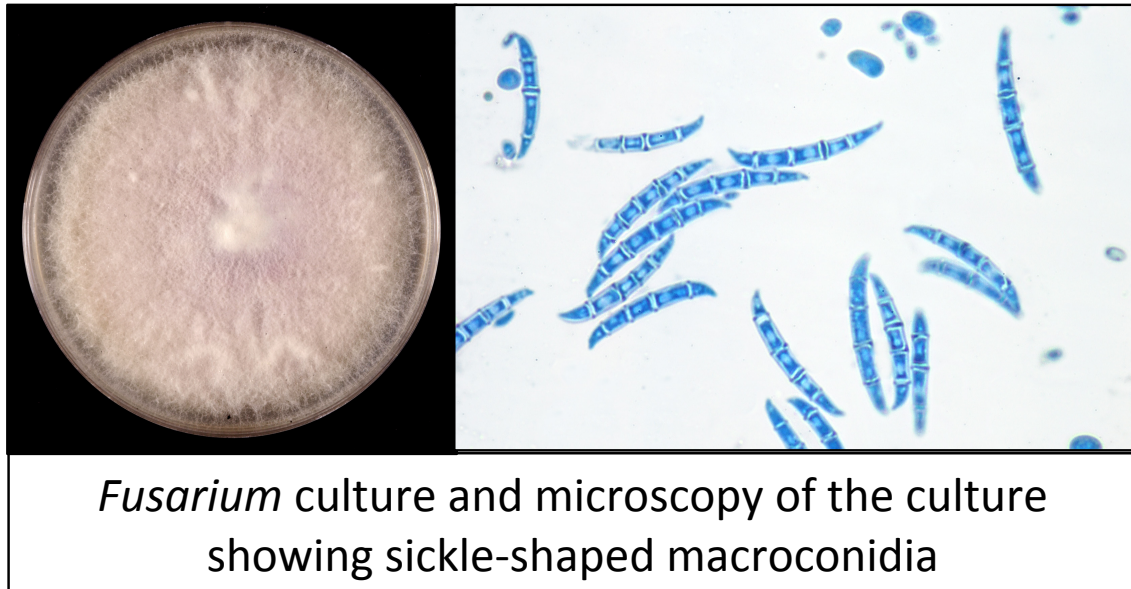
raised slough and colouration other than yellow are statistically more often associated with a fungal cause, whereas immune ring, keratic precipitates, perineural infiltrates, endothelial plaque, and flare or cells in the anterior chamber are not<sup>14</sup>. A probability score of 89% likelihood that the infection is fungal if serrated, feathery infiltrate margins, and raised slough (surface profile) are present, and fibrin is absent from the anterior chamber<sup>5,14</sup>.

## Diagnosis

Diagnosis of fungal keratitis is slow and complicated. Confirmation of the diagnosis is made from corneal scrapings or biopsy, by microscopy and culture<sup>3</sup>. 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 a slit-lamp. As fungi generally penetrate deep into the cornea, the yield of fungi obtained using swabs is usually inadequate to confirm a diagnosis. The material is then transferred to a clean glass microscope slide, flooded with potassium hydroxide and examined for fungal elements by light microscopy. Direct microscopy of corneal smears allows the clinician to rapidly differentiate between a fungal infection and other types of microbial keratitis and is considered the gold standard for diagnosis of fungal infection. The sensitivity for detecting fungal keratitis has been reported to be 61–94% using potassium hydroxide, 85% using lactophenol blue, but just 36–50% using a traditional Gram stain<sup>5</sup>. Calcofluor-white is said to be a mainstay of diagnosis,

and when combined with potassium hydroxide stains, sensitivity has been shown to rise to 98.3%<sup>5</sup>.

It is not possible to differentiate between genera and species of fungi on the basis of microscopic examination of the corneal smear preparation alone. For this reason, it is advised that both microscopy and culture are done whenever possible.



Samples should be cultured on bacterial and fungal media<sup>3,5</sup>. Blood agar, chocolate agar, and Sabouraud dextrose agar are inoculated with corneal scrape material using C-shaped streaks, because of the very small size of the inoculum, and only colony growth within these parameters are regarded significant. 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 cultures<sup>3</sup>. *Fusarium* species are the most common (Fig 4) , 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. Culture negative microbial keratitis is estimated at around 40%<sup>5</sup>. This means a huge underestimation of fungal keratitis burden and an urgent need to improve the diagnostic approach, make it simpler and improve sensitivity.



Other approaches that can be helpful for diagnosis are molecular methods and confocal microscopy but are technically and cost demanding<sup>15</sup>. The molecular tool of choice is PCR, which only requires a small quantity of sample. PCR has been shown to have high sensitivity and specificity when compared with smear stains and culture. PCR positively identifies the causative fungal species in 92.6% of cases<sup>5</sup>. However, the technique is currently of limited use in low resource settings, where the burden of disease is greatest.

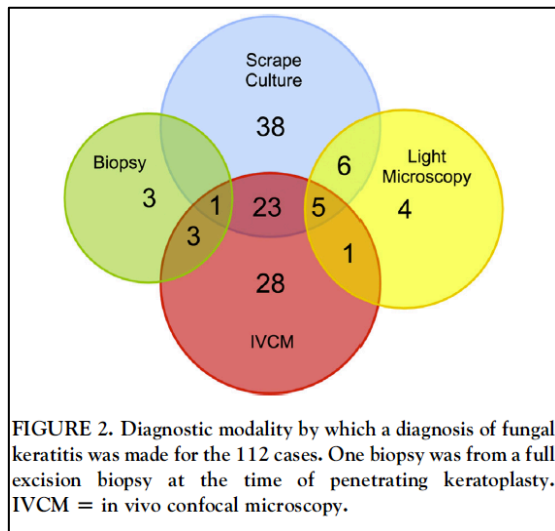


Figure 5. Venn diagram showing how the diagnosis of fungal keratitis was made in London<sup>15</sup>

Point of care testing of this disease would dramatically improve patient outcomes. Slow diagnosis, including referral from one facility to another, worsens visual outcome<sup>16</sup>.

## 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 (Primaricin)<sup>17,18</sup>. Other therapies produce similar response rates, although natamycin is superior to voriconazole<sup>18</sup>. Advanced disease on presentation is associated with worse outcomes.

Natamycin 5% eye drops are not registered as treatment in most [countries](#), and all suppliers are in India. Natamycin eye drops are now listed (2017) as a WHO Essential Medicine. 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%<sup>3</sup>. 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.

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

It has been estimated that 95,000–115,000 eyes are surgically removed each year as a direct result of fungal keratitis<sup>5</sup>. In countries where eye care is suboptimal, the loss of eyes will probably be greater. Using outcome data from the Pakistan study for low-income and middle-income countries, it is predicted that 610,800 eyes will go blind because of fungal keratitis each year<sup>5</sup>.

## 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

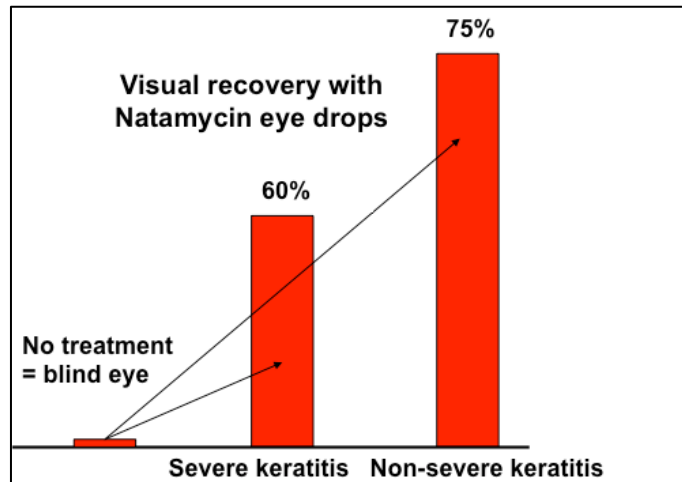


Figure 6. Outcomes from fungal keratitis with natamycin 5% eye drops.

2. Provide training and availability in classical diagnostic procedures including sampling, culture techniques and fungal species identification
3. Optimize use of antifungal therapy in resource limited settings through promoting a global approach to the prevention, diagnosis and management of microbial keratitis
4. Develop a point of care antigen test able to differentiate bacterial infection from fungal infection,
5. Investigate the value of introducing combination treatment with antibiotic and antifungal eye drops versus early diagnosis of the cause and targeted therapy,
6. Ensure that antifungal treatments, especially natamycin eye drops, are readily accessible everywhere
7. Develop prophylactic or pre-emptive treatment guidelines for ocular injuries
8. Deliver training in appropriate delivery of the eye drops, dosing and timing
9. Encourage the performance of clinical trials to determine the best treatment for fungal keratitis.

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