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# Mycotic keratitis: epidemiology, diagnosis and management

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## Abstract

Mycotic keratitis (an infection of the cornea) is an important ocular infection, especially in young male outdoor workers. There are two frequent presentations: keratitis due to filamentous fungi (*Fusarium*, *Aspergillus*, phaeohyphomycetes and *Scedosporium apiospermum* are frequent causes) and keratitis due to yeast-like fungi (*Candida albicans* and other *Candida* species). In the former, trauma is usually the sole predisposing factor, although previous use of corticosteroids and contact lens wear are gaining importance as risk factors; in the latter, there is usually some systemic or local (ocular) defect. The clinical presentation and clinical features may suggest a diagnosis of mycotic keratitis; increasingly, *in vivo* (non-invasive) imaging techniques (confocal microscopy and anterior segment optical coherence tomography) are also being used for diagnosis. However, microbiological investigations, particularly direct microscopic examination and culture of corneal scrape or biopsy material, still form the cornerstone of diagnosis. In recent years, the PCR has gained prominence as a diagnostic aid for mycotic keratitis, being used to complement microbiological methods; more importantly, this molecular method permits rapid specific identification of the aetiological agent. Although various antifungal compounds have been used for therapy, management of this condition (particularly if deep lesions occur) continues to be problematic; topical natamycin and, increasingly, voriconazole (given by various routes) are key therapeutic agents. Therapeutic surgery, such as therapeutic penetrating keratoplasty, is needed when medical therapy fails. Increased awareness of the importance of this condition is likely to spur future research initiatives.

**Keywords:** Azoles, confocal microscopy, culture, direct microscopy, epidemiology, fungal keratitis, mycotic keratitis, polymerase chain reaction, voriconazole

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Mycotic keratitis (International Nomenclature of Diseases disease number 2100) is a general term for a mycosis of the cornea, and can be caused by a wide variety of fungi [1]. This condition is usually manifested by severe inflammation, the formation of a corneal ulcer, and hypopyon, with the presence of fungal hyphae within the corneal stroma. Synonyms include 'keratomycosis' and 'oculomycosis' (in part), but 'mycotic keratitis' is recommended in preference to 'keratomycosis' so as to have similar names for the diseases caused by fungi, bacteria and viruses [1]. If the fungal species causing the infection is identified, a term such as '*Fusarium* keratitis'(or, more specifically, 'keratitis due to *Fusarium solani*') is recommended [1].

## Epidemiology

Epidemiology refers to the study of the distribution and determinants of a disease in a given population in a given period of time. Whereas *prevalence* is the rate or frequency with which the disease is found in a group or population under study at a particular point in time, *incidence* is the frequency with which new cases of a disease arise over a defined period of time [2]. Going strictly by these definitions, there are no published reports on the prevalence of mycotic keratitis in the community, but there is one study, in the UK, that has reported on the incidence of mycotic

keratitis in a community (0.32 (95% CI 0.24–0.44) cases per million individuals per year) [3]. However, in less strict usage, modified for clinical series [2], it is possible to look at the prevalence of mycotic keratitis among individuals presenting with keratitis (corneal inflammation) to a hospital; this provides an estimate of the magnitude of the problem. In this respect, mycotic keratitis may account for more than 50% of all patients with culture-proven microbial keratitis [4,5], especially in tropical and subtropical environments. In terms of absolute numbers, this condition apparently occurs more frequently in developing countries (e.g. China and India) than in the developed world (e.g. the USA, Australia) A single institution in Hyderabad (India) reported that 1360 individuals with culture-proven mycotic keratitis were seen over a period of 10 years and 5 months [6], and another institution in northern China reported 654 patients with this condition over a 6-year period [4]. In contrast, mycotic keratitis was documented in just 56 eyes (56 patients) in Melbourne (Australia) and in 61 eyes (57 patients) in New York (USA) over 8-year and 16-year periods, respectively [7,8].

Although a high incidence of mycotic keratitis might be expected in countries with similar annual rainfall and temperature range, this is not always so and incidence also appears to depend on the extent of urbanization [9]. Mycotic keratitis associated with the wearing of contact lenses may also be on the rise [10] A statistically significant increase in the relative frequency of mycotic keratitis during the years 1997 to 2007 was noted in Egypt; this rise was found to correlate significantly with rises in minimum temperature and the maximum atmospheric humidity in the greater Cairo area over the same period [11]. A review of the data from studies on microbial keratitis conducted worldwide noted that whereas the highest proportion of bacterial corneal ulcers was reported from studies in North America, Australia, the Netherlands and Singapore, the highest proportion of fungal corneal ulcers was reported from studies in India and Nepal; interestingly, the Spearman correlation coefficient demonstrated a statistically significant inverse correlation between gross national income and percentage of fungal isolates in the studies [12]. A study in Brazil sought to predict the epidemiology of mycotic keratitis by monitoring the sales distribution of antifungal eye drops in Brazil; a linear regression model displayed a significant association between reduced relative humidity and sales of antifungal drugs, which was interpreted to mean a seasonal distribution of mycotic keratitis, with a higher incidence during the third quarter of the year (when the climate is drier and when agricultural activity is more intense in Brazil) [13].

## Types and Aetiological Agents of Mycotic Keratitis

In terms of occurrence, risk factors and therapeutic approaches, two basic types of this condition are recognized, namely, keratitis due to filamentous fungi and keratitis due to yeast-like and related fungi (keratitis due to thermally dimorphic fungi has only rarely been reported). There appears to be a strong geographical influence on the occurrence of the different forms of mycotic keratitis. The proportion of corneal ulcers caused by filamentous fungi has shown a tendency to increase towards tropical latitudes, whereas in more temperate climates, fungal ulcers appear to be uncommon and to be more frequently associated with *Candida* species than filamentous fungi [14].

### Keratitis due to filamentous fungi

Filamentous fungal keratitis usually occurs in healthy young males engaged in agricultural or other outdoor work; these fungi do not penetrate an intact epithelium and invasion is secondary to trauma. Trauma is the key predisposing factor, occurring in 40–60% of patients [5,6]; other reported risk factors include previous ocular surgery, ocular surface disease, previous use of corticosteroids (either topical or systemic) and contact lens use [10,15,16]. Interestingly, in one study on mycotic keratitis, response to antifungal therapy and or surgery was observed in none of six patients with previous ocular surgery, two of six patients with previous ocular trauma, two of six patients with ocular surface disease, all three patients with contact lens use and six of 16 patients with previous use of corticosteroids [16]. Traumatizing agents of plant or animal origin (even dust particles) either directly implant fungal conidia in the corneal stroma or abrade the epithelium, permitting fungal invasion [4–6,17,18].

Species of *Fusarium*, *Aspergillus*, *Curvularia* and other phaeohyphomycetes, *Scedosporium apiospermum* and *Paecilomyces* are the principal causes of filamentous fungal keratitis, but many other species have been implicated [18–21] (Table 1). Environmental factors (humidity, rainfall, wind) appear to have a bearing on the occurrence of filamentous fungal keratitis and may also determine seasonal variations in the frequency of isolation of fungi and the fungal species isolated [14]. Along the Gulf of Mexico, keratitis due to *Curvularia* spp. appeared to occur more frequently during the hotter, moister, summer months, possibly because of an increase in airborne *Curvularia* spores during these months [22].

Although *Fusarium* species have been cultured from soft contact lenses during use [23], it was still a surprise when, from mid-2005 to around July 2006, a multi-country outbreak of contact lens-associated keratitis due to *Fusarium* species