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An Overview of Prevalence and Treatment of Mycotic Keratitis in India and other Countries in the Indian Subcontinent

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Abstract

Mycotic keratitis is a sight-threatening disease, caused by infection of the cornea by filamentous fungi or yeasts. This paper reviews data on the prevalence, diagnosis, therapy and prevention of mycotic keratitis in different states in India, and in other countries, namely Pakistan, Nepal, Bangladesh, Sri Lanka and Bhutan, in the Indian subcontinent. In vivo confocal microscopy and molecular techniques(polymerase chain reaction) have improved management of the condition.

Keywords: Keratitis; etiological agents; clinical features; therapy; prevention

Introduction

Corneal blindness is a major public health problem worldwide, being more common in tropical and subtropical regions, and infectious keratitis is one of the predominant causes. A World Health Organization (WHO) report has highlighted that ~6 million of the world population are affected by cornea-related blindness or moderate/severe visual impairment, including 2 million of those who are affected by trachoma[World Health Organization, 2004]. Corneal opacity represents the 5th leading cause of blindness globally, accounting for ~3.2% of all cases[Flaxman et al.,2017].

Keratitis describes a group of acute or chronic inflammatory disorders occurring in the cornea following any factors disrupting the protective mechanism of the outer layer of the eye [Acharya et al., 2017]. The inflammation may be of allergic (reactive), physical, chemical, or infective (bacteria, fungi, parasites, and viruses) origin[Acharya et al., 2017]. Infectious or microbial keratitis is a leading cause of visual impairment and preventable blindness worldwide. Very appropriately, infectious keratitis (IK) is now included among neglected tropical diseases by the WHO[Ung et al., 2019]. Early diagnosis and management are, therefore, essential to prevent long-term complications of blindness [Castano et al., 2024].

Keratitis due to fungi, that is mycotic keratitis or fungal keratitis, is caused by infection of the cornea by filamentous fungi or yeasts. This condition was first documented in 1879, and its incidence is believed to be on the increase. A very recent retrospective observational study on the case reports of 51,747 patients of microbial keratitis seen at the same institution over a 30 year period (1991 to 2020) appears to support this contention; 51.13% of the patients turned out to be culture-positive, with a decrease (from 56% to 38%) noted in the proportion that were bacterial isolates and an increase(from 24% to 51%) noted in the proportion that were fungal isolates over the 30-year period[Joseph et al.,2023]. However, this may also just be a reflection of improving diagnostic acumen over the years with reference to fungal infections.

Mycotic keratitis, which accounts for about 40% to 50% of all IK cases, can, if not properly treated, lead to corneal destruction and endophthalmitis, with severe loss of vision; in tropical, low, and middle-income countries, it accounts for a high proportion of cases of IK [Hoffman et al., 2021]. In 2018, the Asian Cornea Society Infectious Keratitis Study (ACSIKS) included 6626 eyes of 6563 patients from eight Asian countries[Khor et al., 2018]; bacterial keratitis was diagnosed in 38.0% and mycotic keratitis in 32.7%.

Mycotic keratitis is common in warm, humid regions, with a varying profile of pathogenic fungi according to geographical origin, socioeconomic status, and climatic condition. The highest estimated incidences are in Asia and Africa, and the lowest in Europe. On a global scale, a minimum annual incidence of 1,051,787 cases (range: 736, 251 to 1,367,323) has been estimated, with the highest rates being in Asia and Africa[Brown et al., 2021]. If all culture-negative cases are assumed to be fungal, the annual incidence would be 1,480,916 cases (range: 1,036 641 to 1,925,191). It appears that 8-11% of patients have to have the eye removed, which represents an annual loss of 84,143 to 115, 697 eyes[Brown et al., 2021]. With reference to the proportion of cases of suppurative (microbial) keratitis shown to be caused by fungi. India, Sri Lanka, Bangladesh and Nepal have been shown to have a very high proportion (> 45%), while Pakistan has a high proportion of 25 to 45 % [Brown et al., 2021]. Countries where the proportion is > 25 % tend to be near the equator (but not universally so). For some countries, where multiple reports over time have been noted, there appears to be an increasing trend in proportion of all microbial keratitis being diagnosed as mycotic keratitis [Brown et al., 2021]. A significant negative correlation has been found between proportion of patients with microbial keratitis who have proven mycotic keratitis and a logged GDP/capita (although adjusted R2 value is limited at 34%). When multiple regression is used to assess the relationship between the proportion (%) of microbial keratitis patients who have mycotic keratitis and transformed values (log) of both GDP/capita and distance from equator, the resulting scatterplot displays many unexplained variables[Brown et al., 2021].

Monomorphic fungi can be classified into yeast and filamentous fungi, and both are responsible for cases of mycotic keratitis. More than 100 different fungal species can cause mycotic keratitis, and novel pathogens are regularly added [Ahmadikia et al., 2021]. The specific type of fungus responsible depends on several factors, including personal risk factors, regional temperature, climatic conditions, geographic location, and urbanization[Ting et al., 2021]. However, it is clear that the most common fungal species are *Fusarium*, *Aspergillus* and *Candida species*[Ahmadikia et al., 2021]. *Fusarium* spp. and *Aspergillus* spp. thrive in tropical climates, and yeast-like fungi such as *Candida* spp. thrive in subtropical and temperate climates. In the 2018 ACSIKS study referred to above, *Fusarium species* and *Aspergillus flavus* accounted for 18.3% and 8.3%, respectively, of all isolates[Khor et al., 2018]. This study reconfirmed the dominance of *Fusarium* spp. keratitis within China (26%) and India (31%) established two decades ago.

In most IK cases, local and/or systemic risk factors are usually present[Ting et al., 2021]. The most common risk factors include ocular trauma[Khor et al., 2018], contact lens wear[Khor et al., 2018], ocular surface disorders, dry eye diseases, neurotrophic keratopathy, rosacea, lid diseases, post- corneal surgery (e.g. keratoplasty, corneal cross-linking) and systemic diseases (e.g. diabetes, immunosuppression), amongst others. A high index of suspicion is, therefore, usually required, depending on the presence of specific risk factors. It has been hypothesized that posttraumatic IK is initiated following infection of a breach(abrasion) in the corneal epithelium, and that application of antimicrobials to the abraded cornea soon after trauma should reduce the incidence of IK. Two studies at the village level, one in Bhutan[Getshen et al.2006]and one in Burma [Maung et al., 2006] have validated this hypothesis; in the Bhutan study, application of 1% chloramphenicol ointment soon after detection of trauma-induced corneal abrasion effectively prevented bacterial keratitis [Getshen et al., 20062], while in the Burma study, application of 1% chloramphenicol-clotrimazole ointment soon after the corneal abrasion effectively prevented mycotic keratitis[Maung et al., 2006].

Even if the diagnosis is made, management is still challenging, since many antifungal agents have poor penetration into the cornea. The causative organism of mycotic keratitis may differ according to several factors[Ting et al., 2021]. Accordingly, this paper attempts to review data on the prevalence of mycotic keratitis in different states of India, and also in other countries in the Indian subcontinent, namely Pakistan, Nepal Bangladesh, Sri Lanka and Bhutan; the demographic and clinico-mycological features of keratitis in these areas are described. Predisposing factors, including co-morbidities and different type of corneal injuries, are also mentioned. Therapy of keratitis with different antifungal agents and preventive measures are fully discussed.

Methods

An exhaustive search of the literature was made in Google, MedFacts. Medliine, Science Direct, National Centre for Biological Information (NCBI), Google Scholar, Research Gate and Mycology database, using different sets of keywords.

Reports of Mycotic Keratitis from different regions of India

It is to be noted that there are many reports of mycotic keratitis from different parts of India. This review will focus on recent studies and those describing large numbers of patients. In general, the relative prevalence of mycotic keratitis in eastern India is lower than that in southern, western, and north-eastern India, but higher than that in northern India; however, *Aspergillus* and *Fusarium* appear to be the predominant genera associated with mycotic keratitis across India [Sharma et al., 2022].

Mycotic keratitis in Delhi state

In a study based at the All-India Institute of Medical Sciences, New Delhi, on patients with suspected IK, the overall fungal culture positivity was 21.5%, 67.3% of whom were males and 32.7% were females. The maximum number of samples (17.9%) was received from age group 41-50 years, and maximum fungal culture positivity was seen in age group 31-40 years (30.8%) [Satpathy et al., 2019]. The most common fungal isolates were *Aspergillus* species (31.1%), *Fusarium* species (24.5%) and four genera of melanized fungi(cumulatively accounting for 32 % of the isolates)[Satpathy et al., 2019]. Fungal culture positivity and relative frequency of fungi remained almost stable over the study duration, except *Rhodotorula* spp., which showed a rise from 2014 onwards. Highest numbers of culture- proven mycotic keratitis cases were seen in monsoon season [Satpathy et al., 2019].

Mycotic keratitis in Haryana state

In a study spanning 16 years (January 2001-December 2015) at the Post-Graduate Institute of Medical Education and Research, Chandigarh, of 2459 clinically- suspected mycotic keratitis cases, 765 (31 %) cases were confirmed by direct microscopy to be positive. Of these microscopy-confirmed cases, fungi were isolated in 393 (51.4 %), with *Aspergillus* spp. ranked top (n = 187, 47.6 %), followed by melanized fungi (n = 86, 21.9 %) and *Fusarium* spp. (n = 64, 16 %)[Ghosh et al., 2016]. A male predominance of 78.7 % was noted, with a peak incidence of mycotic keratitis during the post-monsoon season (September to November)[Ghosh et al., 2016].

Mycotic keratitis in Uttar Pradesh state

In a study from Varanasi, a diagnosis of mycotic keratitis was made in 41 cases (30 males, 11 females), based on positive direct microscopy(potassium hydroxide[KOH] preparation). When culture was included, among these 41 cases, fungal growth was obtained only in 36 cases whereas the remaining five cases were positive only by KOH mount [Tilak et al., 2010]. Males were more commonly affected and were mostly in the age group of 31-40 years. *Aspergillus flavus* was the most common fungus isolated, followed by *Fusarium solani*. With regard to occupation, 22 of the 41 cases were farmers and labourers; the rest were housewives and students, with one weaver and one serviceman also. Trauma appeared to be the most common predisposing factor, being observed in 17 cases [Tilak et al., 2010].

Mycotic keratitis in Gujarat state

In a study based in Ahmedabad, Gujarat, 73 (35.9%) out of 208 suspected cases were confirmed by culture as cases of mycotic keratitis; all 73 isolates were identified by a study of colony character and microscopic morphology[Gujjar et al.,2013]. The spectra of fungi isolated were *Fusarium* spp. (26.6%), *Aspergillus* spp. (21.6%), and dematiaceous fungi (11.6%). The sequence of the ITS region could identify the *Fusarium* and *Aspergillus* species at the species complex level, and the dematiaceous isolates were accurately identified [Gujjar et al.,2013].

Mycotic keratitis in Telangana/Andhra Pradesh state

Gopinathan et al [2002] performed a retrospective review of the case records of 1,352 cases(1354 eyes) of mycotic keratitis diagnosed at a tertiary eye care facility in Hyderabad, southern India, between January 1991 and December 2000. Males (962) were affected significantly more frequently than females (390). Of 1,352 patients, 853 (64.4%) were in the younger age group (16-49 years). Ocular trauma predisposed to infection in 736 (54.4%) of 1,354 eyes. There was a higher incidence of mycotic keratitis during the monsoon and winter than summer. A fungal cause was established by smears of corneal scrapings in 1,277 (95.4%) eyes. The KOH mount, Calcofluor white (CFW), Gram- and Giemsa-stained smears revealed fungus in 1,219 (91.0%), 1,224 (91.4%), 1,181 (88.2%), and 1,139 (85.1%) eyes, respectively. *Fusarium* (506, 37.2%) and *Aspergillus* species (417, 30.7%) were predominant in the hyaline fungal spectrum (1,133) and *Curvularia* species (39, 2.8%) were the highest among the dematiaceous isolates (218)[Gopinathan et al., 2002].

Interestingly, in a follow-up retrospective study on 51,747 patients with IK seen over a 30-year period at the same institution, a decrease (from 56% to 38%) was noted in the proportion that were bacterial isolates and an increase(from 24% to 51%)was noted in the proportion that were fungal isolates[Joseph et al. 2023].

Mycotic keratitis in Eastern states of India

There are four notable studies of mycotic keratitis in Eastern states, including one each from Tripura state[Das and Chakma, 2016] and Assam state[Nath et al., 2011], and two from Odisha state[Rautaraya et al., 2011, Paty et al., 2016].

In the study from Tripura state, conducted at the department of ophthalmology in a medical college and teaching hospital, 100 samples of corneal scrapings collected from patients with a clinical diagnosis of corneal ulcer(with or without hypopyon) seen over a 12- month period (1/11/2013 to 31/10/2014), were subjected to microbiological investigation to determine the etiological agents[-Das and Chakma, 2016]. Of the 63 culture- positive patients, who were mostly males (68%), 36 (57.1%), had bacterial growth and 27(42.9%) had fungal growth. *Aspergillus* spp. (*Aspergillus flavus A. fumigatus, A. niger*) were the main fungal isolates, followed by *Candida albicans* (7%), *Fusarium solani*(4%), *Penicillium species* (2%), *Rhodotorula* spp(1%) and *Trichosporon* spp(1%)[Das and Chakma, 2016].

In a noteworthy report from upper region of Assam state, 188 cases aged 41-50 years (males 140, females 48) of fungal etiology were diagnosed at the Medical College, Dibrugarh[Nath et al., 2011]. The maximum (23.4%) number of cases were reported during the paddy harvesting season (January and February). Fungal elements could be demonstrated in 65.2% cases in direct KOH mounts. The commonest predisposing factor was corneal injury (74.5%). While diabetes was a significant systemic predisposing factor in mixed bacterial and fungal infections in 11.1% cases, blocked naso-lacrimal duct was the local predisposing factor in 11.1% of cases. *Fusarium solani* was the commonest isolate (25%), followed by species of *Aspergillus*(19%), *Curvularia*(18.5%) and *Penicillium* (15.2%), and by yeasts(2.7%).Most of the cases were rural workers in tea gardens[Nath et al., 2011].

At the LV Prasad Eye Institute, Bhubaneshwar, Odisha state, 997 patients were clinically diagnosed as IK between July 2006 and December 2009; a diagnosis of mycotic keratitis was established in 26.4% (264/997) [Rautaraya et al., 2011]. Two hundred fifteen of 264 (81.4%) samples grew fungus in culture, while 49 corneal scrapings were positive for fungal elements only in direct microscopy. Clinical diagnosis of mycotic keratitis was made in 186(70.5%) of the 264 cases. The microscopic detection of fungal elements was achieved by 10% KOH with 0.1% CFW stain in 94.8% (238/251) cases. *Aspergillus* species (27.9%, 60/215) and *Fusarium* species (23.2%, 50/215) were the major fungal isolates; concomitant bacterial infection was seen in 45 (17.1%, 45/264) cases of mycotic keratitis[Rautaraya et al., 2011].

In another study in Odisha state, conducted at the Dr NTR University of Health Sciences, Bhubhaneshwar, 50 cases (aged 30-40 years) suspected to have mycotic keratitis were investigated [Paty et al., 2016]. A diagnosis of mycotic keratitis was confirmed by direct microscopy in KOH mounts and Gram stain and positive culture on Sabouraud dextrose agar (SDA) in 16 (32%) cases (males 11, females 5) [23]. The most common risk factor was trauma with vegetative matter in 62.5% of cases. The most frequent fungal isolate was *Aspergillus* spp. in 43.75%, followed by *Fusarium*, *Candida*, and *Curvularia* spp. [Paty et al., 2016].

Mycotic keratitis in Maharashtra

A total of 1010 clinically suspected cases of mycotic keratitis were studied from 1988 to 1996 at a medical college in Mumbai; of these, 367 cases were confirmed by microscopy and culture to be of mycotic aetiology. Eighty eight percent of patients were farmers or construction workers and 89.92% of cases gave a definite history of antecedent corneal trauma[Deshpande and Koppikar, 1999]. A single fungal isolate was obtained in 307, multiple fungal isolates in 20 and mixed isolates of bacteria and fungi in 40 of the confirmed 367 cases. The predominant isolates were *Aspergillus* species(219), *Candida* species (36), *Fusarium* species (33) and *Penicillium* species (34), while filamentous fungal isolates from 22 cases remained unidentified[Deshpande and Koppikar,1999].

More recently, a prospective study on 40 patients with corneal ulcer was conducted over a 25 month period (October 2011 to November 2013) at a medical college in Dhule, northern Maharashtra [Kalshetti et al., 2015]. Microbiological tests on corneal scrapings from the patients confirmed a diagnosis of mycotic keratitis in 14; fungal growth in culture was obtained in 12 cases, while the other two were positive only by KOH preparation. *Aspergillus* species and *Fusarium* species were the major isolates. Seven (50%) patients with mycotic keratitis were farmers, three (21.4%) labourers and four (28.5%) were housewives. Corneal trauma was identified as the predominant predisposing factor. Males were more commonly affected and were mostly in the age group of 21 to 50 years[Kalshetti et al., 2015].

Mycotic keratitis in Goa

One hundred and twenty-eight cases of corneal ulcers, clinically suspected to be IK, were investigated by mycological tests at a medical college in Goa[Verenkar et al., 1998]; 74 cases were clinically non -mycotic and did not grow fungi in fungal culture. In 54 patients with a clinical suspicion of mycotic keratitis, a fungal etiology was proven in 21 patients, the incidence of mycotic keratitis being 38.9 %. Fungi were isolated in 16 cases (29.6 %). KOH wet mount showed presence of hyphal elements in an additional 5 cases. *Aspergillus* species, inclusive of *A. fumigatus* (48.7 %) and *A. niger* (12.5 %), were the predominant fungal agents isolated; other fungal isolates included *Fusarium* spp. (12.5 %). *Mucor* spp. (12.5 %), *Penicillium* spp. (12.5%) and *Curvularia* spp. (6.3 %). These authors concluded that in their locality, mycotic keratitis frequently occurred in elderly patients pursuing agricultural occupations, who were exposed to risk of corneal trauma, and that injudicious use of steroids/antibiotic preparations and herbal medicines were contributory factors[Verenkar et al., 1998].

Mycotic keratitis in Rajasthan state

In a study at a medical college in Bikaner, Rajasthan state, between July 2017 to December 2017, a total of 42 clinically suspected cases of corneal ulcer were studied using KOH mounts and fungal culture. [Jajodia, 2018]. Twenty-two (52.38%) samples were positive in KOH mount; fungus was grown in 14 KOH positive samples and in 3 KOH negative samples. *Aspergillus* spp. were isolated in eight cases, *Fusarium* spp. in six cases and *Alternaria* spp. in three cases out of 17 fungal culture-positive cases. Most of the positive cases were aged>50 years; males(13) were more commonly affected than females(4). Most of the patients were farmers and labourers. A history of trauma with plant debris and straws was obtained in 42% of patients. A total of 22% patients received topical antibiotics or corticosteroids. [Jajodia, 2018].

In another, hospital-based study at Jaipur, Rajasthan, Gupta and Rishi[2017] sought to isolate and identify aetiological agents from 96 cases of suspected IK seen over a period of 18 months (January 2015 to June 2016). Microbiological studies on corneal scrapings from the 96 patients revealed a higher prevalence of mycotic keratitis (37, 56.9%) in comparison to bacterial keratitis (28, 43.1%). Out of 96 samples, 37 were positive on fungal culture, 11 were positive on Gram staining and 16 showed hyphae in KOH mount. Of the 37 fungal isolates, *Aspergillus* spp. (23 isolates, 62.2%), *Fusarium* spp (9 isolates, 24.3%), *Curvularia* spp. (4, 10.8%) and *Candida albicans* (1, 2.7%) were identified[Gupta and Rishi, 2017].

Mycotic keratitis in West Bengal state

Saha and co-workers [2009] retrospectively reviewed the charts of 289 patients with IK who attended a tertiary eye care hospital in Kolkata over a one year period (January to December 2008). Of the 289 patients, 110 (38.06%) were diagnosed with mycotic keratitis (10% KOH mount positive). Of the 110 patients, 74 (67.27%) were 10% KOH mount and culture positive. Forty- five of 74 culture-positive patients (60.81%) were in the older age group (>50 years) and males were more commonly affected. Agricultural activity- related ocular trauma in 35 cases (47.29%) was identified as a high risk factor, and vegetative injuries in 17 cases (22.97%) were identified as a significant cause for mycotic keratitis. Maximum organism source was from corneal scrapings in 41 cases (55%). The predominant fungal species isolated were *Aspergillus* spp. (55.40%), *Candida albicans*(18.91%) and *Fusarium* spp.(10.81%). Although 30(40.55%) of the 74 culture- positive patients healed with corneal scar formation following medical treatment, unfortunately, 44 cases (59.45%) required therapeutic keratoplasty[Saha et al., 2009].

Study of mycotic keratitis in Tamil Nadu state

Over a 3- month period at a tertiary care eye hospital in Madurai, 434 patients with central corneal ulceration were evaluated; 284 (65.4%) of these 434 patients gave a history of previous corneal injury. Of the 434 patients, 297 patients (68.4%) yielded pure cultures of etiological agents[Srinivasan et al., 1999]. Of these, 139 (46.8%) had pure fungal infections and 15 (5.1%) had mixed bacterial-fungal infection. The most common fungal pathogens isolated were Fusarium spp. (47.1% of all positive fungal cultures) and *Aspergillus* spp. (16.1%)[Srinivasan et al., 1999].

In a subsequent study from 2002 to 2012 at the same institution, 23,897 patients of IK were investigated; although no organisms were noted in corneal smears in 38.3% of cases, fungal organisms were noted in 34.3% of cases and bacterial organisms in 24.7%[Sun et al., 2014]. Interestingly, during this period, the annual number of bacterial keratitis cases decreased from 677 to 412 while that of mycotic keratitis cases increased from 609 to 863. In analyses accounting for the total number of outpatients seen each year, the decline in number of smears positive for bacteria was statistically significant but the increase in the number positive for fungus was not [Lalitha et al., 2014].

The influence of traditional healers in patients with corneal injuries during agricultural labour was highlighted by Nirmalan et al. [2004]. They found that 107(46.9%) of 229 persons who reported ocular trauma sustained the same during agricultural labour; moreover, 37(20.6%) of the 229 sought treatment from a traditional healer. Although seeking treatment from a traditional eye healer for trauma was not associated with vision impairment (OR, 1.0; 95% CI, 0.3-3.2) or with blindness (OR, 3.4; 95% CI, 0.2-56.5), the authors advocated simple measures, such as education regarding the use of protective eyewear, to significantly decrease this preventable cause of visual disability[Nirmalan et al. 2004].

Study of mycotic keratitis in Karnataka

In a study at a medical college in Manipal, fungi were isolated from 67 of 295 cases of suspected IK; species of, *Aspergillus* and *Candida* were the major fungal isolates[Kotigadde et al., 1992]. Interestingly, a higher incidence of mycotic keratitis was seen among females than males. No relationship to seasonal changes could be established. Bacterial infection was associated in 46.27% of the cases of mycotic keratitis, with *Staphylococcus* being the predominant bacterial pathogen observed[Kotigadde et al., 1992].

Study of mycotic keratitis in Kerala

In a study in 2017 at a medical college in Thiruvananthapuram, 100 patients (68 males, 32 females, aged 10-80 years) with clinically- suspected mycotic keratitis were evaluated; the diagnosis was confirmed in 56 by observation of fungal hyphae in KOH mounts of corneal scrapings and by positive cultures on SDA, blood agar and MacConkey agar [Cherian et al., 2017]. The main fungal pathogens isolated were *Aspergillus* in 22 cases (*A. flavus*-10, *A. fumigatus* -6, *A. niger* -6) and *Fusarium* spp. in 9; several other genera and species were also isolated. Most of the patients were manual labourers, housewives or students. Diabetes mellitus was a major predisposing factor [Cherian et al., 2017].

Reports of mycotic keratitis from different countries in the Indian subcontinent

Mycotic keratitis in Pakistan

In a study based in southern Pakistan, out of 240 patients presenting with corneal ulcer during a 24 month period (April 2006-March 2008), mycotic keratitis was diagnosed in 84 (35%) patients above 15 years of age [Narsani et al., 2009]. Among these 84 patients, 48 (57.1%) were males and 36 (49,1%) were females; 60(71.4%) belonged to rural population while 24 (28.6%) had an urban background. Interestingly, *Candida abicans* was the main causal agent isolated in 74 (78.6%) of the 84 patients; other fungal agents were *Aspergillus flavus* in eight (9.5%) patients and *Penicillium* in two (2.4%) patients. Corneal trauma was the major predisposing factor[-Narsani et al., 2009].

Reports of mycotic keratitis in Bangladesh

Out of 142 cases of suppurative keratitis referred to Chittagong Eye Infirmary, 53.5% of cases were bacterial and 35.9% were fungal. The most common fungal pathogens were *Aspergillus* sp. (13%), *Fusariurn* sp. (7%) and *Curvularia* sp. (6%); Gram stain and culture results were consistent in 62.6% of cases[Dunlop et al., 1994]. On Gram stain, 55.9% of pseudomonal cases were missed, but only 2% of fungal cases were missed. Overall, Gram stain had a sensitivity of 98% and positive predictive value of 94% for fungal cases. Fungal ulcers were typically filamentous, but an antecedent history of trauma was not common. The most frequent injury was due to rice grains, but the inoculum appeared to be introduced during eye washing with contaminated water. *Fusarium* cases were seen only in the dry season[Dunlop et al., 1994].

Reports of mycotic keratitis in Nepal

In 1991, Upadhyay et al [1991] lamented that while the incidence of IK was around 113 per 100,000 in India, it was as high as 799 per 100,000 in Nepal; moreover, patients with corneal ulcers usually visited the physician for treatment only after the infection was well- established some weeks to months later. This was especially the case with fungal ulcers that could be devastating. Corneal trauma in fungal, bacterial or mixed infections was mostly caused by paddy, dust, maize, grass, wheat and wood [Upadhyay et al, 1991]. Recently, there have been two notable reports of mycotic keratitis in different regions of Nepal. In one report, patients presenting with keratitis to a tertiary eye hospital in lowland eastern Nepal from June 2019 to November 2020 underwent in vivo confocal microscopy and corneal scrape for microscopy and culture; fungal etiology was identified in 482/642 (75.1%) and fungal and bacterial mixed etiology was identified in an additional 50 cases[Hoffman et al., 2022]. Unusually, dematiaceous fungi accounted for half of the culture-positive cases (50.6%). Serrated infiltrate margins, patent nasolacrimal duct, raised corneal slough, and organic trauma were independently associated with mycotic keratitis [Hoffman et al., 2022]. In the other study, in a hospital in Lahan, 174 patients(88 males and 86 females)were evaluated[Puri et al., 2022]. Ocular trauma with vegetative matter was reported by 79 (45%) and 84 (48%) had fungal infections. Visual acuity was $<3/60$ in 107 (61%) of affected eyes at presentation, reducing to 73 (42%) at last follow-up. Factors associated with poor visual outcome in mycotic keratitis were trauma with vegetative matter, delayed presentation and poor visual acuity at presentation; 126 patients (72%) were farmers[Puri et al., 2022].

Reports of mycotic keratitis in Sri Lanka

Over a two-year period (1976-1977 and 1980-1981), 66 cases of bacterial and mycotic cases of keratitis were diagnosed at the General Hospital in Kandy, Sri Lanka. The fungal etiologic agents isolated and identified were *Aspergillus flavus*, *A. niger*, *Fusarium oxysporum*, *Lasiodiplodia theobromae* and *Paecilomyces farinosus*[Gonawardena et al., 1994]. In vitro the fungi showed sensitivity, in decreasing order, to flucytosine, nystatin, amphotericin B and econazole. Due to the out-patient status of the patients, patients' in-vivo response to treatment was not assessable[Gonawardena et al., 1994].

Diagnosis of Mycotic Keratitis

A fungal corneal ulcer classically presents as a dry, raised lesion with crenate or feathery borders, presence of satellite lesions and a hypopyon. In a study in Nepal, Hoffman et al. [2022] observed that serrated infiltrate margins, patent nasolacrimal duct, raised corneal slough, and organic trauma were independently associated with mycotic keratitis. However, clinical diagnosis can be challenging in difficult cases and those refractory to treatment[Maharana et al., 2016].

Conventional methods for the diagnosis of mycotic keratitis include staining of tissue scrapings with Gram-stain, 10% KOH wet mount, lactophenol cotton blue, Giemsa, or CFW [Gugnani et al., 1978]. KOH is one of the most commonly performed direct microscopy procedures for detection of fungi, since it is a rapid and inexpensive procedure. It has a sensitivity of 61-94% and specificity of 91-97% for detecting fungus. SDA is a very commonly used culture medium for isolating fungi [Gugnani et al., 1978; Gugnani, 2021]. Fungal hyphae on microscopic examination and culture isolation have been the gold standard in the laboratory diagnosis of mycotic keratitis. Isolation of the etiological fungus in culture is essential to perform antifungal susceptibility testing, but it is time-consuming, causing delays in the initiation of treatment[Gugnani et al., 1978; Gugnani, 2021].

Over the last decade, a number of newer methods have been devised for detection of fungi[Maharana et al., 2016]. In vivo confocal microscopy allows the direct visualization of fungal hyphae or yeast cells in the corneal tissue without the need for obtaining a sample by invasive techniques(corneal scraping or biopsy)[Hoffman et al., 2022].

Molecular diagnostic methods have recently gained popularity because they permit a rapid diagnosis of fungal keratitis. Genomic approaches are based on detecting amplicons of ribosomal RNA genes, with internal transcribed spacers being increasingly adopted. PCR has emerged as a sensitive and specific test for the diagnosis of fungal keratitis. Various studies have compared PCR with conventional diagnostic methods in cases with suspected fungal keratitis. PCR has the highest positive detection rate overall, especially in cases with culture or smear-negative results[Maharana et al., 2016]. Metagenomic deep sequencing allows for rapid and accurate diagnosis without the need to wait for the fungus to grow. This is also helpful in identifying new emerging strains of fungi causing mycotic keratitis [Kuo et al., 2019]. A custom-tear proteomic approach will probably play an important diagnostic role in future in the management of mycotic keratitis[Kuo et al., 2019].

Management of mycotic keratitis

The incidence of mycotic keratitis is higher in developing countries, compared with that in developed countries[Brown et al., 2021. This may be because trauma to the eyeball and therapy with antibiotics and corticosteroids render the eye susceptible to infection with various fungi, especially in tropical parts of the world Compared with other cause of IK, mycotic keratitis has a poor prognosis, due not only to lack of effective treatment (drugs and methods), but also because fungi are different from other pathogens in pathogenesis[Niu et al.,2020]. Mycotic keratitis presents various challenges to the treating physicians, such as delayed presentation, long waiting time for culture positivity, limited availability of effective antifungal drugs, prolonged duration for response to therapy, a highly variable spectrum of anti-fungal drug sensitivity and a high recurrence rate following keratoplasty[Sharma et al., 2022]. The advent of rapid diagnostic tools, molecular methods, in vitro anti-fungal drug sensitivity testing, alternatives to natamycin, targeted drug delivery and ,most importantly, the results of large randomized controlled trials have significantly improved our understanding and approach towards the diagnosis and management of cases with mycotic keratitis [Hoffman et al., 2022].

Currently available antifungal agents for treatment include amphotericin B for both yeasts and filamentous fungi, natamycin for filamentous fungi, miconazole for both yeasts and filamentous fungi and econazole for filamentous fungi. Oher agents include ketoconazole a broad spectrum antifungal agent, fluconazole for *Candida* species, flucytosine, caspofungin, miconazole for yeasts, and voriconazole for yeasts and moulds[Sharma et al., 2022; Maharana et al., 2016; Hoffman et al., 2022].

Natamycin has been tried for treatment of several cases of mycotic keratitis [Jones et al., 1972]. Natamycin (pimaricin), as a 5% suspension, was mentioned to be effective in successful therapy in 16 of 18 cases of consecutive *Fusarium solani* corneal ulcers between February 1969 and January 1971, with 13 of these patients obtaining a visual result of 20/40 or better[Jones et al., 1972]. These results compared favorably with a series of 20 *Fusarium ulcers* treated with amphotericin B prior to February 1969. Amphotericin B was effective in eliminating the fungus in only seven patients, five of whom retained a visual acuity of 20/40 or better.

Natamycin is an approved first-line drug. Voriconazole is the best alternative, especially for non-fusarium cases Management involves administration of drugs usually by a combination of various routes, with the treatment regimen being individualized depending upon the response to therapy [Sharma et al., 2022; Maharana et al., 2016]. Intrastromal injection of voriconazole has been found to be a good therapeutic adjunctive for the management of deep recalcitrant fungal keratitis[Sharma et al., 2022]. Photodynamic therapy is a newer treatment modality, being tried for non-responsive cases, before resorting to a therapeutic graft [Maharana et al., 2016].

Recently, MICs of natamycin and voriconazole to fungal isolates from a relatively large number of cases in Tamil Nadu have been reported[Lalitha et al., 2014]. The response to medical treatment was poor in patients with late presentation. The MIC median (MIC50) and MIC90 for natamycin were equal to or higher than for voriconazole for all organisms, except *Curvularia* species. Compared to other organisms, *Fusarium* species isolates had the highest MICs to voriconazole and *A. flavus* isolates had the highest MICs to natamycin. The result of this study reinforces the previous finding of mycotic ulcer topical treatment trial (MUTT) and that for non-tuberculous mycobacteria that natamycin is better than voriconazole[Sun et al., 2014]. Association between in vitro susceptibility to natamycin and voriconazole and clinical outcomes in fungal keratitis has been reported[Sun et al., 2014].

Using antifungal agents, such as fluconazole, natamycin, amphotericin B, and itraconazole, the minimum inhibitory concentrations (MICs) for *Fusarium* spp. were >32 μ g/mL, 4-8 μ g/mL, 0.5-1 μ g/mL, and >32 μ g/mL, respectively [Gujjar et al., 2013]. Antifungal susceptibility data showed that *Curvularia* spp. was highly resistant to all the antifungal agents. Overall, natamycin and amphotericin B were found to be the most effective antifungal agents[Gujjar et al., 2013]. The comparative clinical outcomes in all cases showed that the healing response in terms of visual acuity of the dematiaceous group was significantly good when compared with the *Fusarium* and *Aspergillus* groups[Gujjar et al., 2013].

Rautarya et al [2011] have described their results in treating 264 patients with mycotic keratitis at a tertiary eye care facility in Odisha. Topical antifungal therapy with 5% natamycin was started for all cases; systemic ketoconazole (200 mg twice daily), itraconazole (100 mg twice daily) or fluconazole (150 mg once a day) was prescribed to 158 (58.3%) patients with corneal stromal infiltrate extending beyond one third of the depth of the cornea. Additional procedures for patients not responding to medical treatment included therapeutic penetrating keratoplasty (TPK), evisceration, and cyanoacrylate glue application with bandage contact lens(BCL) or anterior chamber wash with amphotericin B [Rautarya et al., 2011]. A good clinical outcome, namely a healed scar, was achieved in 94 (35.6%) of the 264 cases; 52 patients (19.7%, 52/264) required TPK, nine (3.4%, 9/264) went for evisceration, 18.9% (50/264) received glue application with BCL for impending perforation, 6.1% (16/264) were unchanged and 16.3% (43/264) were lost to follow up. A poor prognosis, such as PK (40/52, 75.9%, $p < 0.001$) and BCL (30/50, 60%, $p <0.001$) was seen in significantly larger number of patients with late presentation (> 10 days) [Rautarya et al., 2011].

Saha et al.[2009], at Kolkata, West Bengal, reported that 30 (40.55%) of their 74 culture- positive patients healed with corneal scar formation with medical treatment whereas 44 cases (59.45%) required TPK.

Most of the currently available antifungal medications have limitations, such as poor bioavailability and limited ocular penetration especially in cases with deep-seated lesions. Hence, there is the need to explore other options as well[Lalitha et al., 2007]. Various published case reports have shown posaconazole to be an effective agent against *Fusarium* keratitis that was resistant to other antifungals[Tu et al., 2007; Altun et al., 2014; Sponsel et al., 2002]. Posaconazole was used either systemically, alone or in combination with topical posaconazole suspension, in these studies. The dosage of oral posaconazole was 200 mg four times daily or 400 mg twice a day in these studies, while the dosing schedule of topical formulation was 10 mg/0.1 ml and 4 mg/0.1 ml with hourly topical ocular application[Tu et al., 2007; Altun et al., 2014; Sponsel et al., 2002]. All cases had severe fungal keratitis with associated endophthalmitis and were resistant to routinely used antifungals including voriconazole. Posaconazole use resulted in rapid resolution of infection in these cases without significant toxicity [Tu et al., 2007; Altun et al., 2014; Sponsel et al., 2002]. Thus, it can be assumed that posaconazole can be used in cases of mycotic keratitis that are resistant to standard antifungal therapy. However, a few issues still need to be addressed. The use of topical posaconazole alone (without use of the oral preparation) needs to be investigated further. There is a difference in the reported concentration of the topical formulation. 10 mg/0.1 ml of posaconazole has been used in one study [Sponsel et al., 2002] and a concentration of 4 mg/0.1 ml of posaconazole in another, more recent, study[Altun et al., 2014]. The safety and efficacy need further study, including study of a large number of cases.

Very recently, Hoffman et al. [2022] suggested a treatment protocol for filamentous mycotic keratitis. On presentation, the cases are to be treated with topical 5% natamycin; if the ulcers are greater than 5mm in diameter or affect more than 75% of corneal depth, systemic antifungals such as ketoconazole or voriconazole are advocated. It was suggested that if natamycin was not available, topical chlorhexidine(0.2%) could be used on presentation. If the response to topical natamycin or chlorhexidine was good, topical therapy could be continued; if not, it was suggested to add topical 1% voriconazole. If the response was poor, it was suggested to try targeted injections or to resort to surgery (TPK)[Hoffman et al., 2022]. These workers also suggested that chlorhexidine could be used as an adjunctive agent to natamycin, and that topical amphotericin B 0.15% could be considered when other agents are not available, or as an adjunctive agent in challenging cases [Hoffman et al., 2022]. These suggestions require further evaluation.

Early therapy is essential in minimizing damage to the corneal tissue, thereby providing a better outcome. The role of conventional therapy with polyenes, systemic and targeted therapy of antifungal agents, newer azoles and echinocandins in mycotic keratitis has been widely studied in recent times [Castano et al., 2024]. Combination therapy can be more efficacious in comparison to monotherapy.

Positive repeat cultures are being suggested as an important gauge indicative of a poor prognosis. Positive repeat fungal cultures help to modify a treatment regimen by increasing its frequency, providing the addition of another topical and oral antifungal agent along with close follow-up for perforation and identifying need for early TPK[Kuo et al., 2019]. Role of collagen cross linking in the treatment of mycotic keratitis is not convincingly established. Rapid detection by multiplex PCR and antifungal susceptibility testing of the pathogenic fungi, adopted into a routine management protocol of mycotic keratitis, will help to improve treatment outcome[Kuo et al., 2019].

Prevention of mycotic keratitis

Prevention, early diagnosis and early treatment of mycotic keratitis can undoubtedly improve the curative effect and the prognosis of patients and reduce the blindness rate. Therefore, it is of great clinical significance and social value to study the preventive methods, pathogenesis and diagnosis of mycotic keratitis[Niu et al., 2020]. A history of ocular trauma and contact lens wear, as well as other clinical factors, need to be considered before diagnosis. More than 70 fungal species can cause sight-threatening keratitis, the pathogenesis of which involves morphological changes, adhesion, ocular trauma, virulence factors and immune evasion. Mycotic keratitis is difficult to treat, due to the scarcity of antifungal drugs. The emergence of drug-resistant fungal strains and the lack of corneal donors necessitate the early diagnosis and prevention of mycotic keratitis[Niu et al., 2020].

Mycotic keratitis tends to affect outdoor workers due to the possibility of ocular trauma; however, corticosteroid use and contact lens usage are also key predisposing factors[Castano et al., 2024]. Farmers should be educated regarding the dangers of mycotic infections and should be advised to wear protective safety glasses to avoid dust and minor trauma to the eyes. Introduction of mechanical devices in agricultural occupations may minimize the incidence of mycotic ulcers. Personal cleanliness in washing hands before touching eyes is essential to avoid fungal infections from other parts of the body[Castano et al., 2024].

To prevent post-operative infections and possibility of infection during operations, care should be taken to avoid air-borne organisms, spores in glove powder, inadequate sterilization of instruments by soaking in contaminated solution and drugs, and presence of fungi in the ocular and periocular tissues of the patient. Pre-operative prophylaxis with antifungal agents, such as povidone iodine or amphotericin B eye drops, is advocated. Routine antibiotic program and lavish postoperative steroid therapy should be reorientated and should be used with great caution as both are double edged swords[Castano et al., 2024]. Routine use of fungicidal sprays in the operating room is desirable. Rigid operating room cleanliness by modern methods should be adopted to see that no dust is stirred up during cleaning. Precautions against contamination of fungi from outside agencies, such as street dust, shoes and other uncovered clothing, should be rigidly followed [Maharana et al., 2016].

Thiabendazole has been found to be a good antifungal agent in preventing mycotic keratitis following corneal trauma[Gugnani et al., 1978; Gugnani, 2021]. It has been found that corticosteroids and antibiotics used indiscrimi-nately in the presence of other non-pathogenic or pathogenic microorganisms can convert a non-pathogenic fungus into a pathogenic one or increase the virulence of pathogenic fungi[Puttana, 1969].

Since posttraumatic IK is initiated following infection of a breach(abrasion) in the corneal epithelium, then application of antimicrobials to the abraded cornea soon after trauma should reduce the incidence of IK. This concept has been validated by two village-level studies, as referred to earlier[Getshen et al., 2006; Maung et al., 2006]. The situation in Burma is exceptional. Two thirds of all culture positive corneal ulcers grow fungal organisms and coupled with the high incidence of corneal infection in the country, the blinding sequelae for the population are disastrous. Application of 1% chloramphenicol-clotrimazole ointment soon after the corneal abrasion effectively prevented mycotic keratitis[Maung et al., 2006]. Because the incidence of bacterial keratitis and mixed infections is also high, all corneal abrasions should be treated prophylactically with antibiotic ointment.

Village health workers(volunteer or otherwise), a fairly extensive rural health network and a campaign (either official or by word of mouth) to publicize the fact that individuals with abrasions could seek treatment with the health workers, are also key ingredients of a successful preventive strategy. It may also be important to solicit the cooperation of traditional healers in these defined populations,

Future directions in prevention and treatment of mycotic keratitis

Diagnosis of keratomycosis on clinical suspicion is 63-83% and by microscopic examination of corneal scrapings in KOH mount is 91%. This still highlights the limitation of routine clinical examination and smear examination, which is not performing 100% efficiently. It is for 37%, 17% and 9% of cases, every day advanced technologies are called for [Shukla et al., 2008]. Those who deal with patient care are aware of certainties and uncertainties of results of clinical examination. The best reported figures at specialized centers might not translate into clinical practice. Another factor to be kept in mind is that many patients who come after secondary and tertiary referrals are already treated with antibiotics, antivirals, steroids and sometimes even antifungals that distort the clinical picture completely[Shukla et al., 2008]. There is need for formulating effective and affordable antifungal combinations for early treatment of corneal ulcers caused by fungi. combinations for early treatment of corneal ulcers caused by fungi. Further, preventive chemotherapy should be instituted in individuals like farmers, carpenters and other categories of workers, particularly in rural areas, who frequently sustain corneal injuries. Fungal infection is only a part of the overall problem of the loss of eyes from suppurative keratitis. It should now be possible to produce a combined antifungal antibacterial preparation for widespread and immediate prophylactic first aid use after corneal trauma, especially in rural areas. Similarly, as mycotic keratitis probably affects over a million people annually, an inexpensive, simple diagnostic method and affordable treatment are needed in every country [Brown et al., 2021]. Surveys are however needed in collaboration with primary health centers for use of combined antifungal antibacterial preparation as a prophylactic first aid use after corneal trauma, especially in rural areas. These studies may require provision and distribution of kits for diagnostic cultures.

Conclusion

This paper reviews the prevalence of mycotic keratitis in different states of India and other countries in the Indian subcontinent. An update on this and preventive measures are also provided. The information provided in our study is only a tip of the iceberg of burden of mycotic keratitis. World-renowned centers of ophthalmic research in India should explore this problem with a missionary zeal; they should also, in collaboration with primary health centers in urban and rural areas, undertake surveillance of cases of myotic keratitis to develop measures for its treatment and prevention with low-cost medicines. There is need for exploring antifungal therapy by herbal drugs by our mycologists and physicians.

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Author Contributions

Both authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Harish C Gugnani and Philip A Thomas. The first draft of the manuscript was written by Harish C Gugnani and both authors commented on previous versions of the manuscript. Both authors read and approved the final manuscript.

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