Guest Editorial

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Insights into recent perspectives on fungal keratitis

Mycotic keratitis is most often seen in warm, humid regions. Fungal keratitis constitutes about 50% of infectious keratitis in the developing world with about 25% of affected patients requiring surgical interventions.[1] The etiology of fungal keratitis varies with geographical origin, socioeconomic status, and climatic condition. Aspergillus spp. and Fusarium spp. seem to be more common in tropical and subtropical regions and infections with Candida spp. predominate in the temperate regions. The most common fungi isolated from our centre included Aspergillus species (31.1%), followed by Fusarium species (24.5%), Alternaria (10.5%), Curvularia (10.2%), Helminthosporium (5.7%), Bipolaris (5.4%), Penicillium (4.5%), Candida (4.4%), Acremonium (1.2%), Rhizopus (1.0%), Paecilomyces (0.8%), Rhodotorula (0.5%) and Mucor (0.2%).[2] The fungal organism's virulence and bioburden, host defense mechanism and immune response along with inadequate diagnostics and treatment strategies are largely responsible for the resultant morbidity.

The randomized controlled Mycotic Ulcer Treatment Trial (MUTT) I noted topical natamycin to be beneficial over topical voriconazole for fungal ulcers, especially in Fusarium ulcers. MUTT II results also did not favor the use of oral voriconazole as improved overall outcomes were not seen in the study.[3] Positive repeat cultures are being seen as an important gauge indicative of a poor prognosis. Positivity of cultures repeated at six days following antifungal therapy in the MUTT I and II were found to be at a higher risk for the therapeutic keratoplasty and a worse three-month visual acuity, and a larger scar size[4,5] Repeat cultures is a useful tool for prognosticating and identifying fungal keratitis who might benefit with a therapeutic keratoplasty done early. Positive repeat fungal cultures should prompt treating clinician to intensify treatment regimen with increasing frequency, addition of another topical and oral antifungal agent along with close follow-up for perforation and need for early therapeutic keratoplasty. Repeat cultures are more helpful to establish the efficacy of new antifungal agents in comparison to time to healing or visual outcome. The role of collagen crosslinking in treatment of fungal keratitis is yet to be convincingly established.

Detection of fungal hyphae in KOH mounts is still the mainstay diagnostic approach in the management of fungal keratitis in several parts of India and other developing nations. In-vivo confocal microscopy aids in early institution of antifungal therapy with timely detection of fungal hyphae by real time corneal imaging. Culture growth of the causative fungus, though time consuming, is essential for species identification. Culture isolate of the etiological fungus also helps to perform antifungal susceptibility testing to establish the sensitivity to treatment with conventional and newer antifungal agents. In the setting of conventional diagnostic approaches (clinical diagnoses, smears, and cultures) failing to provide reliable diagnosis, refractory mycotic keratitis can result in poor prognosis.

Molecular diagnostic techniques now help to obtain a rapid diagnosis of fungal keratitis. Recently recommended omics approaches, such as those using genomic, metagenomic, and tear proteomic data sources, seem to provide greater hope for better diagnosis and follow-up of fungal keratitis cases. Genomic approaches are based mainly on detecting amplicons of ribosomal RNA genes, with internal transcribed spacers being increasing adopted in clinical practices. Recent sophisticated metagenomic approach is based on 16S rRNA genes to help monitor the dynamic change of conjunctival microbial flora associated with fungal keratitis episode. Diagnostics based on 18S rRNA target enrichment sequencing have been suggested to have good potential to diagnose fungal corneal infections using clinical samples.[6]

Application of recent diagnostic methods will help to enhance the precision of diagnosis in fungal corneal infections. Metagenomic deep sequencing (MDS) allows for rapid diagnosis and more effective for obtain an accurate diagnosis without

the need for waiting for the fungus to grow. This is also helpful in identifying new emerging strains of fungi causing mycotic keratitis. However, it should be noted that MDS is not FDA approved and also not in routine use. A tear proteomic approach has also been hailed to provide comprehensive data on ocular surface defense and damage due to mycotic keratitis. Custom tear proteomic approach will probably play an important diagnostic role in future in the management of mycotic keratitis. Future strategies to reduce the morbidity associated with infectious keratitis are likely to be multidimensional, with adjuvant therapies aimed at modifying the immune response to infection holding the greatest potential to improve clinical outcomes

The treatment portal of fungal keratitis has just a few available antifungal preparations with only natamycin, amphotericin B, voriconazole, itraconazole and fluconazole. Fusarium and Aspergillus predominate as the most common cause of mycotic keratitis with regional differences. It is to be noted that Fusarium isolates seem to display a higher antifungal resistance than Aspergillus strains against most of the common antifungal agents.[7] Rapid detection by multiplex PCR and antifungal susceptibility testing of the pathogenic fungi will enable optimal tackling of virulent pathogenic fungi with institution of therapy with the appropriate antifungal agent. Early therapy is essential in minimizing damage to the corneal tissue, thereby providing a better outcome. Recent literature reports better efficacy of combination therapy in comparison to monotherapy.[8] Newer antifungal agents are being found useful in refractory cases of mycotic keratitis though their use in standard protocol is still not warranted considering the emerging concern of resistance to antifungal agents.[9] Given the diversity of fungal etiology, emergence of new corneal pathogenic fungi with varying drug susceptibilities, increasing drug resistance to antifungal agents in some genera and species, the time to adopt recent molecular methods for precise identification and incorporate antifungal susceptibility testing as a routine has perhaps come.

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