Fungal keratitis is an important cause of vision loss in developing countries, and while its prevalence has been increasing over the past few decades, the recent outbreak of contact lens-associated Fusarium keratitis has drawn attention to these serious infections seen by ophthalmologists worldwide.

Never antifungal compounds have shown promise for delivering better treatment, and authors of a recent study evaluating the in vitro susceptibility of clinical fungal keratitis isolates in India suggest greater use of voriconazole (Vfend, Pfizer) in particular may afford better outcomes. Currently, fungal keratitis remains a perplexing diagnostic challenge and a difficult management problem for ophthalmologists.

“Knowledge of the risk factors for fungal keratitis and its clinical characteristics are important to enable prompt diagnosis and appropriate care. Medical therapy remains empiric, but understanding of the aetiology of these infections and the differing susceptibility profiles of common pathogens to antifungal agents can help guide selection of effective treatment,” Denise de Freitas MD, Department of Ophthalmology, Federal University of Sao Paulo, Brazil, told EuroTimes.

The principal risk factors for fungal keratitis are similar worldwide and include presence of ocular surface disease, prior therapy with a topical corticosteroid or antibacterial agent, ocular trauma (especially involving exposure to organic material), and a history of contact lens wear.

The most common causative pathogens for these infections include the yeast Candida albicans or either of the filamentous moulds, Fusarium spp. or Aspergillus spp., although the prevalence of these organisms as clinical isolates in fungal keratitis varies geographically. Aspergillus spp. and Fusarium spp. are the most common isolates in fungal keratitis cases in the eastern hemisphere, and Fusarium infections have also been common in the southern U.S. Historically, Candida has predominated in northern states, although the recent outbreak of Fusarium keratitis in contact lens wearers has caused a shift in the epidemiology.

The patient’s history together with clinical appearance at the slit-lamp may suggest the diagnosis of fungal infection. Hallmark features of infections caused by filamentous fungi include a lesion with irregular feathery margins, dry rough texture, and presence of satellite lesions. In more advanced cases, there may be anterior chamber inflammation, hypopyon, endothelial plaque, ring infiltrate, Descemet’s folds, and keratic precipitates. Yeast infections are more likely to mimic bacterial keratitis. They are characterised by more circumscribed lesions with an overlying epithelial defect and have a slow progression.

The diagnosis of fungal keratitis can often be made by direct microscopic evaluation of material obtained through corneal scraping using simple methods, including KOH, Gram or giemsa stains, calcofluor white, or modified GMS. Culture represents the definitive mode of pathogen identification. Using appropriate inoculation media, 97 per cent of positive cultures will show evidence of fungal growth within one week. Histopathological examination of a specimen obtained by corneal biopsy may be performed if the diagnosis of fungal infection is suspected but the culture is negative.

“Confocal microscopy represents a newer non-invasive tool that is fully diagnostic of fungal keratitis but is not available to most ophthalmologists. PCR modalities are also being developed and appear very promising, although their specificity and sensitivity are variable to date,” said Mark Mannis, MD, who spoke on behalf of Dr de Freitas at the 2007 Joint Congress of the European Society of Ophthalmology and the American Academy of Ophthalmology (SO/AAO).

 Currently, a typical antifungal regimen for treatment of keratitis caused by filamentous fungi may involve hourly administration of topical natamycin five per cent combined with oral itraconazole 200mg bid. Subconjunctival voriconazole 10mg or miconazole 10mg may be added in severe unresponsive infections. For yeast infections, the regimen would include topical amphotericin B 0.15 per cent every hour with oral itraconazole or fluconazole 100mg bid and subconjunctival fluconazole 1.0-2.0mg if needed.

“This polynye’s natamycin and amphotericin B have been the mainstays for treating these difficult infections for decades. Natamycin is well tolerated, whereas toxicity limits the concentration of amphotericin B that can be applied topically as well as its use subconjunctivally. In addition, both natamycin and amphotericin B are large molecules with only limited penetration into the cornea,” noted Dr Mannis, professor and chair, Department of Ophthalmology & Vision Science, University of California, Davis.

Results of a small case series suggested a possible role for intracameral amphotericin B in the treatment of deep keratomycosis. In addition, a newly available, systemically administered preparation of amphotericin in a liposomal formulation (Ambisome) has been shown to have enhanced corneal bioavailability and less toxicity compared with conventional amphotericin B (Fungizone) or amphotericin B lipid complex (ABLC) and may offer a useful alternative in the future for treating fungal keratitis.

Other newer antifungal agents that have been used off-label to treat fungal keratitis include voriconazole, which has broad-spectrum antifungal activity, and has been associated with success when used both topically and orally for the treatment of infections caused by Candida and Aspergillus. Caspofungin (Cancidas Merck), an echinocandin compound, has a favourable safety profile and has been effective in treating corneal fungal infections caused by Candida and Aspergillus. There have also been encouraging reports of the use of another echinocandin, micafungin (Mycamin), applied topically or as a subconjunctival injection to treat refractory corneal ulcers caused by Candida and with the oral triazole posaconazole (Nockafi) in refractory Candida and Aspergillus infections.

Although there has been a trend toward the increasing use of corticosteroids early in the management of bacterial keratitis, their role for managing inflammation in fungal keratitis is controversial. For yeast infections, topical corticosteroids may be started after specific antifungal treatment has been initiated although it has been recommended that their use be avoided entirely in eyes with filamentous fungal infection or at least delayed until after the antifungal therapy has sterilised the film. In addition, it is important to taper the corticosteroid treatment to avoid rebound inflammation that can occur following abrupt discontinuation.

Surgical therapy plays a role in the management of fungal keratitis both as an adjunct to medical therapy for initial management and when medical therapy fails. “Surgical debridement of the epithelium and base of the fungal ulcer is important in the management because it debulks the organisms as well as necrotic material from the cornea to enhance drug penetration,” Dr Mannis said.

Cheryl Guttman

Study provides insight on therapeutic selection for fungal keratitis

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