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Review Article

New Trends on Mycotic Keratitis

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ABSTRACT

Mycotic keratitis, a severe corneal infection predominantly caused by filamentous fungi such as Fusarium, Aspergillus, and Candida, remains a major contributor to ocular morbidity worldwide. Recent trends highlight an alarming rise in cases linked to uncommon fungal species, particularly in tropical and subtropical regions, where incidence may reach 60% of microbial keratitis. Epidemiological data reveal strong associations with agricultural trauma, contact lens use, and prior corticosteroid exposure. Advances in diagnostics have shifted toward rapid, non-invasive techniques, including polymerase chain reaction (PCR), metagenomic sequencing, and in vivo confocal microscopy, which significantly improve early detection compared to traditional culture methods. Therapeutically, natamycin continues as the first-line agent, but resistance patterns and poor drug penetration necessitate innovative strategies. Emerging approaches include intrastromal and intracameral antifungal delivery, combination regimens (e.g., voriconazole with terbinafine), and adjunctive procedures such as corneal collagen cross-linking and photodynamic antimicrobial therapy. Despite these developments, surgical intervention—primarily therapeutic keratoplasty—remains essential in refractory cases, with repeat grafts often required for persistent infections. Global health concerns persist due to limited access to advanced diagnostics and antifungal agents in high-burden regions. Future directions emphasize personalized therapy guided by antifungal susceptibility testing, integration of molecular diagnostics, and cost-effective interventions to reduce vision loss. These innovations collectively aim to improve prognosis and address the unmet needs in managing this neglected tropical disease.

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1. Introduction

Fungal keratitis is a rare form of infectious keratitis, the diagnosis and treatment of which still represent a complex challenge for the ophthalmologist.

The greater virulence of these pathogens and the greater risk of corneal perforation are well known, compared to other forms of infectious keratitis [1].

The highest incidence rates are recorded in developing countries, particularly in regions with a tropical climate, where positive cultures for fungi are found in 21-62% of all cases of microbial keratitis.

In Italy and in all countries with a temperate climate, the incidence rates are markedly lower, with positive cultures for fungi in 1-5% of cases of infectious keratitis. In the largest epidemiological studies carried out to date, a variable incidence of 0.32-1.53 cases per million inhabitants has been estimated [2].

In relation to the etiological agents, we can distinguish two distinct clinical forms: Keratitis caused by filamentous fungi (Fusarium and Aspergillus) and keratitis caused by yeasts (Candida).

Keratitis caused by filamentous fungi is very common in regions with a tropical climate, while in temperate climate regions, infections caused by Candida are prevalent.

However, several studies have shown that the microbial spectrum has been changing in recent years, highlighting a clear increase in keratitis caused by Fusarium and filamentous fungi even in countries with a temperate climate.

Ocular trauma is the main risk factor for the development of fungal keratitis, especially in developing countries.

In Europe and the United States, the use of contact lenses, ocular surface diseases, corneal surgery, and prolonged use of topical steroids are the most common predisposing risk factors [4].

There is also a correlation between the etiological agent and the cause of fungal keratitis. It has been shown that keratitis secondary to trauma is most commonly due to Aspergillus, the secondary forms to ocular surface diseases to Candida while Fusarium prevails in the secondary forms to contact lenses.

Alterations of the ocular surface allow microorganisms to enter the deeper corneal layers. This invasion triggers an immune reaction, both innate and acquired, which leads to the consequent cicatricial damage and corneal opacities. The invasion of the deep stroma can also result in corneal perforation, extension of the infection to the anterior chamber and to the sclera; in such cases, eradication of the microorganism becomes dramatically difficult [3].

Early diagnosis therefore remains imperative in order to reduce the disabling sequelae of these infections.

Although rare, the pathology is particularly severe, requiring corneal transplantation in 12-48% of cases, and enucleation in 6% of cases [8].

2. Clinical and Diagnosis

An early diagnosis is essential in order to obtain a complete recovery or at least limit the damage.

A detailed collection of the clinical history and the meticulous search for predisposing ocular and systemic factors are of primary importance [5].

A clinical history of ocular trauma, in particular with plant material, or neurotrophic keratopathy, herpetic keratopathy, exposure keratopathy, dry eye keratopathy, or the chronic use of contact lenses and topical steroid drugs, must be paid attention to and can support the suspicion of a fungal infection.

A picture of severe ocular inflammation and opacity of the corneal surface with a dense gray-whitish stromal infiltrate that may be ulcerated or raised is evident. The margins of the lesion may be rounded or irregular and cottony with the presence of pseudo-hyphae. Often the infiltrates are multiple, with satellite lesions, this being an

important diagnostic factor. Sometimes a ring infiltrate, Descemet's folds and, in the most severe cases, anterior chamber reaction and hypopyon may be found.

In the presence of a suspicious clinical picture, it is necessary to perform tissue sampling for direct microbiological examination and culture. Considering the tendency of fungi to grow in the deep corneal layers, superficial sampling is generally inadequate. Therefore, corneal scraping with a surgical blade or platinum spatula is recommended for collecting the corneal sample for analysis [7].

A direct examination with a fresh smear on a slide allows for rapid information, and can be performed with Gram and Giemsa stains that allow for the recognition of yeasts and hyphae, respectively.

Less common is the use of potassium oxide ink, Lactophenol cotton blue and stains with calculofluor white.

The main media used for the isolation of fungi are blood agar, chocolate agar or Sabouraud-dextrose agar. In 83% of cases, fungal growth occurs after 72 hours, and within a week in 97%, which can therefore cause a diagnostic delay.

No culture medium offers a diagnostic sensitivity of 100%, so a negative culture does not exclude the diagnosis.

The antimycogram then allows for the evaluation of the in vitro sensitivity of the isolated pathogen to the various antifungal agents tested. The strong positive correlation between a high MIC value and the risk of perforation has also been demonstrated.

Polymerase chain reaction (PCR) is a rapid, sensitive and specific diagnostic test for the diagnosis of fungal keratitis. In a retrospective study conducted on fungal keratitis over a 10-year period, a sensitivity of 92.6% was highlighted, with a diagnosis that can be made between 4 and 8 hours [9,10].

Confocal microscopy is a non-invasive diagnostic tool that allows direct and rapid visualization of fungal hyphae.

In a prospective study, a specificity of confocal microscopy in the diagnosis of fungal

keratitis of 93% and sensitivity of 89% was estimated.

The limits of this method are essentially the high costs and limited diffusion, as well as being operator dependent.

3. Medical and Surgical Treatment

Antifungals are the drugs of choice for the treatment of fungal keratitis, often combined with topical antibiotics to control bacterial superinfections, as well as cycloplegic eye drops.

Antifungal drugs are essentially classified into four groups: polyenes, imidazoles, triazoles and fluorinated pyrimidines. These drugs are used for topical, oral or intravenous use. The most commonly used for topical use are Natamycin 5% and Amphotericin B 0.15%. Among the new generation drugs we find Voriconazole 1%.16 In some studies, the efficacy of Chlorhexidine for topical use has also been validated [11].

It is important to remember the potential toxic effects of topical antifungal eye drops, such as: punctate keratitis, recurrent epithelial erosions, chemosis and conjunctival hyperemia.

The initial choice of antifungal drug must take into account the results obtained by direct microscopic examination, clinical data, and culture, and whether these allow the diagnosis to be oriented towards an infection by filamentous fungi or supported by yeasts.

In the presence of filamentous fungi, Natamycin 5% is currently the drug of choice, while in the presence of yeasts, Amphotericin B 0.15% and Voriconazole 1% should be considered.18

We must therefore distinguish between non-specific medical treatment with broad-spectrum antifungal drugs and targeted antifungal treatment.

Once the pathogen has been identified through culture, the therapeutic regimen can be modified if necessary, taking into account the data relating to the sensitivity of the pathogen to the various antifungal agents.

Natamycin 5% is currently the most widely used topical antifungal.

It is in fact the only topical antifungal for which, in some countries (not including Italy), a commercial preparation is available (Natacyn 5%, Alcon®). There is no oral Natamycin preparation.

For keratitis caused by Fusarium and Aspergillus, it is the drug of first choice. However, it is limited by poor penetrability towards the deep stroma.

In deep corneal ulcers, it is therefore necessary to carry out an additional adjuvant treatment, possibly subconjunctival, oral or intravenous.

Voriconazole 1% is a new generation triazole [2,13].

It has acquired popularity above all for its ability to penetrate the deep stromal tissue, and for its spectrum of action capable of covering Candida species as well as filamentous agents.

The MUTT I study is a randomized double-blind clinical trial, which compared the efficacy of Natamycin 5% and Voriconazole 1% in the treatment of fungal ulcers, on 323 patients. The results of this study demonstrate better benefits in the group treated with Natamycin in terms of both visual acuity and reduced risk of perforation.

These results were also confirmed in a second large clinical trial, as well as in a recent Cochrane review.

The superiority of Natamycin 5% is most evident in the treatment of Fusarium forms. However, Voriconazole 1% could represent a first-choice drug in patients at high risk of candida infections, although in association with drugs that offer valid coverage against other fungal species.

Amphotericin B belongs to the polyene class, active against Candida and Aspergillus species. However, it offers poor coverage against the spectrum of filamentous fungi. Furthermore, its high corneal toxicity profile is well known, causing punctate epithelial erosions and occasionally a greenish coloration of the cornea. [12]

For these reasons, Amphotericin B 0.15% does not represent a first-choice drug where other more effective antifungal agents are available.

Both Amphotericin B 0.15% and Voriconazole 1% do not exist in commercial eye drop formulations, therefore they must be specifically prepared in galenic form.

As regards the available systemic treatments, we find Voriconazole for oral administration. The rationale for systemic treatment is to achieve a constant drug concentration in the corneal stroma and aqueous humor.

The MUTT II clinical trial evaluated the efficacy of adjuvant treatment with oral Voriconazole, demonstrating no advantage over placebo either for the risk of perforation or in terms of visual acuity.

However, an advantage was demonstrated in the subgroup of Fusarium ulcers.

Among other types of adjuvant treatment, subconjunctival administration of Voriconazole has shown an enhancement in the treatment of deep ulcers treated in addition to topical Natamycin 5%.

Intracamerular injection of Amphotericin B can be used in addition to hypopyon drainage.

The intravenous use of Amphotericin B is limited by the high dose-dependent toxicity (especially nephrotoxicity) [14].

Surgical treatment is necessary in forms of mycotic keratitis that are poorly responsive to medical therapy or where there is a descemetocele with a risk of imminent corneal perforation. The goal of surgical treatment is to eliminate the infectious elements and reduce the immunological reaction against them as well as the removal of necrotic tissue.

Surgical treatments used for small and superficial ulcers include debridement of infected tissue, superficial keratectomy and tarsorrhaphy. In the presence of severe lesions at risk of major complications, conjunctival resurfacing or penetrating keratoplasty are necessary if the responsible agents do not recede under therapy.

Corneal Cross-Linking (CXL) thanks to the photochemical activation of riboflavin, allows the formation of collagen bridges, thus reinforcing the stromal lamellae.

This treatment can have its own value in infectious keratitis thanks to both the direct antimicrobial action and the strengthening of corneal tissues against enzymatic degradation. There is ample evidence in the literature that supports the use of CXL in the treatment of filamentous fungal keratitis.

However, in vitro studies have not demonstrated the ability of CXL alone to inactivate fungi. Only one study that combined CXL and Amphotericin B demonstrated in vitro inactivation of fungi [15].

4. Galenic Preparation of Antifungal Eye Drops

Voriconazole 1%

Method: 200 mg of Voriconazole powder (preparation for parenteral use) are dissolved in 20 ml of saline solution to obtain 20 ml of Voriconazole at a concentration of 10 mg/ml.

Storage: The preparation must be stored at 4°C and must be shaken carefully before each instillation.

Amphotericin B 0.15%

Method: 50 mg of Amphotericin B powder (preparation for parenteral use) are dissolved in 20 ml of sterile saline solution. From this preparation, 3 ml are taken and added to 7 ml of ready-made eye drops (artificial tears type).

Storage: The preparation must not be exposed to light. Periodic inspection of the preparation is necessary as any turbidity is a sign of contamination or precipitation of the same.

5. Conclusions

Recent advances in the understanding of fungal keratitis have significantly reshaped our approach to its diagnosis, treatment, and prevention. The integration of molecular diagnostic tools, such as PCR and next-generation sequencing, has enhanced the speed and accuracy of pathogen identification, enabling earlier and more targeted interventions. Moreover, the discovery of novel antifungal agents and drug delivery systems—such as nanocarriers and intracorneal implants—offers promising avenues for overcoming traditional therapeutic limitations, including poor ocular penetration and resistance.

Emerging insights into host-pathogen interactions and the role of the ocular microbiome have also opened new research frontiers, suggesting that immunomodulatory therapies may complement antifungal regimens in the future. However, despite these encouraging developments, challenges remain, particularly in resource-limited settings where access to advanced diagnostics and treatments is constrained.

Continued interdisciplinary research, global surveillance, and equitable access to innovation will be essential to reduce the burden of fungal keratitis worldwide and to translate these scientific breakthroughs into improved clinical outcomes.

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