Antifungals in eye infections: drugs and routes of administration

Antifúngicos em infecções oculares: drogas e vias de administração

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ABSTRACT

Treatment of fungal eye infections represents a challenge to the ophthalmology practice. For an adequate therapeutic response, besides correct drug choice, it is necessary an effectively administration. This script gathers information about the major antifungal drugs used in eye infections, their concentrations and main administration routes.

Keywords: *Antifungal agents/therapeutic use; Fungal eye infections; Mycoses; Yeasts; Filamentous fungi*

RESUMO

O tratamento das infecções oculares por fungos representa um desafio à prática oftalmológica. Para obtermos resposta terapêutica adequada, além do uso da droga correta, é necessária a administração desta de forma eficaz. Este manuscrito reúne informações a respeito das principais drogas antifúngicas utilizadas em infecções oculares, suas concentrações e principais vias de administração.

Descritores: Antimicóticos/uso terapêutico; Infecções oculares fúngicas; Micoses; Leveduras; Fungos filamentosos

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INTRODUCTION

Fungal eye infections are important causes of ocular morbidity. Since the first report of a fungal keratitis by Leber in 1879[1], an increasing number of cases has been observed. Factors such as corticosteroid use, which facilitates the penetration of pathogens, and the popularisation of topical antibiotics, which create an environment of lower competition among microorganisms on the ocular surface, as suggested as key factors for such increase.

Despite the emergence of new drugs, cure remains difficult in many cases. Compared to antibacterials, antifungals have a lower efficacy due to their mechanism of action (usually fungistatic, with fungicidal action being dose dependent), lower tissue penetration, and the indolent nature of the infection[4].

This paper aims to present information on the main antifungals currently used for the treatment of fungal keratitis and endophthalmitis, highlighting their advantages and disadvantages in order to facilitate the choice of the most appropriate therapy for each case.

POLYENES

This class of antifungal agents includes amphotericin B (AMB), nystatin and natamycin (NTM). Nystatin has not been used to treat eye infections for several decades due to its low tissue penetration, toxicity, and reports of resistance[5,6]. However, AMB and NTM remain as the primary drugs in the treatment of fungal eye infections.

- Amphotericin B

AMB belongs to the family of polyene macrolide antibiotics and was the first broad-spectrum antifungal agent to be discovered. Isolated in the 1950s, AMB is produced by the actinomycete *Streptomyces nodosus*. It became popular after approval by the FDA in the 1960s due to its great efficiency in controlling disseminated fungal infections[4,6-8]. In ophthalmology, it is still the reference drug.

AMB acts by increasing cell permeability through the formation of pores or channels in the fungal cell membrane upon binding to ergosterol and by promoting oxidative action on cells, thus altering their metabolic functions. It also binds to cholesterol in human cells, which is the main reason for its side effects[8,9].

The drug's name is derived from its amphoteric properties (soluble in extreme pHs, both acidic and basic). It has low water solubility and needs to be diluted in deoxycholate for administration. AMB has long molecules that, when infused, coalesce into a colloid. It is photo- and thermosensitive and should be stored in a dark and refrigerated place (2-8°C)[4,6,7,10]. Its action is primarily fungistatic, with fungicidal action depending on the concentration reached in the target tissue[11].

In internal medicine, its use is limited due to its toxicity and side effects. During infusion, fever, chills, hyperventilation, hypotension, nausea, and vomiting may occur, among others. It always causes tubular injury with loss of kidney function in patients with previous kidney disease. It is also partly eliminated by the liver[8,11,12]. AMB should not be diluted in saline solution, as aggregation of colloids can occur, thus reducing the drug's bioavailability.

AMB acts on both yeasts and filamentous fungi. It has an excellent spectrum, being effective against *Candida* spp., *Aspergillus* spp., *Penicillium marneffei*, *Criptococus* spp. and the causative agents of mucormycosis. It is also effective, to a lesser extent, against the main *Fusarium* species. It has no antibacterial activity[4].

AMB also promotes immunopotentiation by binding to cholesterol on the cell membrane of lymphocytes. Suppressor T lymphocytes have higher concentrations of cholesterol in their cell membrane than B and T helper lymphocytes, therefore AMB leads to a reduction in suppressor cells with a relative increase in pro-inflammatory cells[13,14].

Systemic administration of AMB produces little penetration into ocular tissues and does not reach therapeutic levels in the cornea, aqueous or vitreous humour[4,10,15-17]. Furthermore, its side effects discourage systemic administration. Direct in situ administration is therefore the main form of treatment. It is one of the few drugs described in the literature as being used through the subconjunctival, intrastromal, intracameral, and intravitreal routes, as well as topically.

Topical administration in concentrations of 1.5 to 5 mg/ml is commonly the first choice in the treatment of fungal keratitis. The product has to be prepared from the intravenous formulation (Fungizone™ - Bristol-Meyers Squibb, New York, NY) diluted in distilled water. It is used at hourly intervals at the beginning of treatment, and then every 4 hours after the therapeutic response is observed. Periodic debridement of the corneal epithelium is recommended during treatment, because the molecule's large size hinders penetration into the cornea if the epithelium is intact. After topical administration of AMB in rabbits whose corneal epithelium had been removed, therapeutic levels were reached in the corneal stroma. However, in corneas with intact epithelium, concentrations were low or undetectable[18-21]. The drug showed good tolerability and efficiency when used both as eye drops and ointment[22,23].

Subconjunctival administration can be used in patients with low adherence to treatment, but it is limited due to reports of conjunctival necrosis, scleritis and scleral thinning[24,25].

Intracorneal administration, on the other hand, provides better results. There are few reports of complications with this route of administration; also, it provides higher and more sustained corneal concentrations than topical or intracameral administration. Several cases of keratitis unresponsive to topical treatment are successfully resolved after intrastromal administration[18,26], but further controlled studies are still needed. Intrastromal administration of AMB at a concentration of 5 to 10 ìg is suggested for deep infections affecting the stroma that do not respond well to topical treatment[2]. The interval between doses should be at least seven days and the drug should be administered under peribulbar block, as it causes intense pain. Doses above 15 to 20 ì g can cause endothelial cell loss and persistent corneal oedema[18].

Intracameral injection can also be used at a concentration of 5 to 10 ì g/0.1ml. It is administered at least once daily, due to the rapid removal of the drug, without significant endothelial loss. It is indicated in deep infections that penetrate Descemet's membrane and affect the anterior chamber and/or the lens. There are reports of cataract after administration and of a transient increase in chamber reaction within 24 hours due to the immunopotentiating effect of AMB. Other side effects such as iritis and corneal oedema may occur, but they are reversible[27-31].

For the treatment of fungal endophthalmitis, intravitreal injection of AMB is the therapy of choice. The recommended dose ranges from 1 to 10 ì g/0.1ml and may be repeated weekly. In vitrectomised patients, the dosing regimen should be reduced to every 3 or 4 days[32]. Clinical and experimental studies demonstrate the safety and efficacy of this route of administration; however, there are reports of toxicity and retinal necrosis, which are probably dose dependent[3,33].

In eye infections caused by yeasts (especially *Candida* spp.), AMB is still the drug of choice. Although therapeutic success depends on using the drug for a long period (at least 4 weeks), there are few reports of drug resistance by these organisms[34]. Among filamentous fungi, especially *Fusarium* spp., there are reports of drug resistance[3,10].

- Natamycin

Similar to AMB, natamycin (NTM) or pimaricin is a polyene antifungal used only in the treatment of fungal keratitis. It is also used as a pesticide and as a preservative in the food industry [3,35].

NTM has a long molecule with low water solubility. Presented as a suspension, it needs to be shaken before administration. It is the only drug approved by the Food and Drug Administration (FDA) for the treatment of fungal keratitis. In some countries, the drug is commercially available (Natacyn™, Alcon Laboratories, Fort Worth, TX). In Brazil, it needs to be compounded[3,10].

Used at a concentration of 5% (50 mg/ml), it had good stability and is well tolerated when used topically. Due to its high molecular weight, NTM has low corneal penetration and is only indicated as a monotherapy in the treatment of superficial infections[10,36]. In deep infections or those involving intraocular structures, NTM should be associated with other antifungal agents using a different route of administration[2,37-39].

Due to its low corneal penetration, therapeutic success requires long term use of the drug, averaging 39 days[37]. Epithelial debridement is recommended as an adjuvant therapy so that higher concentrations can be achieved in the corneal stroma. This provides a greater adherence of the drug to the de-epithelised surface [3,40]. However, in a study by Prajna et al. epithelial scraping did not improve healing time. In fact, in this study epithelial scraping was associated with lower visual acuity after healing[41].

The dosing interval is similar to AMB, and can be increased once symptoms improve. Some infections require sustained treatment for longer periods; doses every 4 hours maintain therapeutic concentrations in the cornea with good long-term tolerability[42].

Subconjunctival administration is discouraged due to serious complications, such as scleritis and conjunctival necrosis[3,24,43]. There are no reports of administration of NTM through other routes (intracameral, intravitreal, intrastromal, or systemic).

NTM is a broad-spectrum agent, especially against filamentous fungi. Although NTM can also be used in yeast infections, AMB remains the drug of choice due to its wider spectrum against *Candida* species[39,44].

Fusarium infections are usually treated successfully with NTM, especially superficial infections[45,46]. Lalitha et al., in a comparative study on the minimum inhibitory concentrations (MIC) of different antifungal agents, reported that NTM has a lower relative MIC than AMB both against *Fusarium* and *Aspergillus* species[47]. In another clinical trial comparing the efficacy of NTM versus voriconazole (VCZ), no difference was found between the two groups in terms of healing time and final visual acuity [41]. Kalavathy et al. compared the efficacy of NTM and fluconazole (FCZ) and found better results in the group treated with NTM, although the difference was not significant[45]. Several other studies also highlighted the superiority of NTM in the treatment of infections by *Fusarium* spp.[48-50]. Nevertheless, certain authors have shown that about one third of *Fusarium* infections do not respond to NTM[37,51,52]. In such cases, NTM should be replaced by or associated with another drug.

AZOLES

Introduced into medical practice in the 1970s, azoles represented an important advance in antifungal therapy. Compared to AMB, they have a broader spectrum of action and cause fewer adverse effects. Their use spread rapidly, especially in the treatment of infections of the skin and mucous membranes[8].

Azoles act on fungal cytochrome P450 enzymes by blocking the synthesis of ergosterol in the plasma membrane, thus inhibiting fungal growth. Azoles are divided into two major classes — imidazoles were the first to be introduced, followed by triazoles. Both have similar antifungal spectra, but triazoles have the advantages of being metabolised more slowly and exerting less influence on the metabolism of steroids in humans[4,8]. These drugs are metabolised primarily in the liver, therefore control of liver enzymes is recommended. They have teratogenic activity (class C) and should not be used during pregnancy[4,53].

The imidazoles used more often in ophthalmology include miconazole (MCZ), econazole (ECZ) and ketoconazole (KCZ). Among the first-generation triazoles, the most used are itraconazole (ICZ) and fluconazole. Second-generation triazoles were introduced into clinical practice in the past decade and include voriconazole and posaconazole (PCZ).

- Miconazole

MCZ has been developed for use as a topical cream to treat diseases of the skin and mucous membranes and is used primarily in the treatment of superficial mycoses. It is effective against several strains of *Candida*, being used primarily in the treatment of dermatophitosis and oral and vaginal candidiasis, due to its rapid fungicidal action[54]. Systemic administration produces good results but is in disuse due to its cardiovascular and hepatotoxic side effects[55,56].

MCZ not only acts on the synthesis of ergosterol, similar to other azoles, but also promotes the inhibition of peroxidases, resulting in an accumulation of free radicals in the fungal cytoplasm which leads to cell death[57-60].

Topical use at a concentration of 10 mg/ml has good penetration, particularly if associated with epithelial scraping[61-63]. Topical MCZ was also effective in an experimental study where therapeutic concentrations were maintained even with less frequent dosing[64]. It is notably effective and safe when used subconjunctivally (1.2 to 10 mg) in the treatment of infections caused by *Candida*, *Fusarium*, *Curvalaria*, and *Aspergillus*[2,61,65,66]. Systemic use does not reach therapeutic corneal concentrations and is discouraged due to its adverse effects[61,67].

Compared to polyenes, MCZ is less effective but provides better penetration into ocular tissues[5,61]. In vitro, it was more effective than KCZ and ICZ against *Aspergillus* spp., *Candida albicans* and non-*albicans*[50,68]. Further comparative controlled studies are needed to demonstrate the real benefits of this drug.

- Econazole

ECZ, an imidazole with a similar molecular structure to MCZ, is used primarily in the treatment of superficial mycoses, with some studies involving systemic use[69].

It has been little studied in the treatment of eye infections, but there are some reports of topical administration to treat fungal keratitis. In a controlled clinical trial comparing eye drops of ECZ 2% (20 mg/ml) with NTM 5%, there was no statistical difference between the rates of therapeutic success in the two groups; both groups had with good results with no reports of adverse reactions[42]. Mahashabde et al. suggest the use of ECZ ointment 1% as prophylactic treatment after ocular trauma with risk of fungal infection[70]. Unfortunately, the drug is not com-

mercially available for ophthalmic administration, which prevents its use.

- Ketoconazole

KCZ was the first systemic imidazole to be used successfully, but its use is now uncommon in internal medicine. It has been replaced by ICZ due to the latter's milder influence on the metabolism of glucocorticoids and extended antifungal spectrum[4]. It is used at a dose of 100 to 400 mg every 12 hours; its oral absorption depends on gastric pH (below 3), therefore it should be taken without food or gastric acid-suppressive agents. It can be associated with gastric intolerance, hepatotoxicity, gynecomastia, and menstrual changes[8,10].

Although its penetration into the cerebrospinal fluid and urine is low, its penetration into ocular tissues is significant when used systemically. There are numerous reports of therapeutic success with oral KCZ with or without topical NTM or AMB in the treatment of fungal keratitis. Some authors suggest its routine use in all cases of fungal keratitis[71-73], but this is not supported by controlled studies.

There are reports of cases treated exclusively with topical KCZ (10 to 50 mg/ml)[74], but other drugs have been shown to be superior in comparative studies. Komadina et al. and Singh et al., comparing topical and oral KCZ with NTM, showed that the latter is superior. A partial response was also achieved with isolated oral administration, with increased effect when combined with topical NTM[75,76].

In vitro studies with strains of *Aspergillus* spp. and *Fusarium* spp. exhibited a lower susceptibility of these organisms to KCZ compared to NTM and VCZ[50]. Other laboratory studies also showed similar results with strains of *Aspergillus*, *Fusarium* and *Candida* spp., which were susceptible to KCZ only at high doses[34,77].

Currently, systemic KCZ is indicated only for the adjuvant treatment of deep fungal keratitis.

- Itraconazole

ICZ is more frequently used in general practice than KCZ and has fewer side effects when administered systemically. However, when administered orally it exhibits lower bioavailability, solubility and penetration into ocular tissues than other azoles[3,10,78,79]. Similar to KCZ, gastric absorption depends on a low pH. Studies in rats showed that ICZ has a lower teratogenic risk than KCZ[53].

Systemic administration at 400 mg/day was effective in the treatment of infections by *Candida* spp.[80]. However, in infections by *Fusarium* spp., some studies suggest that ICZ is ineffective. Topical use at a concentration of 10 mg/ml was not as effective as NTM 5%[45]. In vitro studies found that ICZ had a higher MIC than AMB and NTM[48,78], and even found some drug resistance among all analysed strains[47]. ICZ was effective against *Aspergillus* spp., but not as effective as KCZ[77].

Systemic use should be limited only to the adjuvant treatment of eye infections by yeasts.

- Fluconazole

Unlike ICZ and KCZ, FCZ shows excellent absorption from the gastrointestinal tract and is not influenced by gastric acidity. Its plasma concentrations with oral use reach almost the same levels as with intravenous administration. Penetration into ocular tissues is effective, reaching aqueous concentrations similar to those in the plasma[4,81].

Oral use at 200 to 400 mg per day was effective in the treatment of eye infections, with or without topical NTM[82,83]. When used subconjunctivally in association with topical AMB, a broader antifungal spectrum was observed with less toxicity than isolated AMB[84]. Yilmaz and Maden managed to treat 60% of cases of fungal keratitis with subconjunctival injections of FCZ alone[85]. A subconjunctival dose of 2 mg in 1 ml administered daily for 10 days is recommended, followed by every 48 hours until remission[86].

FCZ eye drops achieved good intracorneal therapeutic levels against strains of *Aspergillus fumigatus* in rabbits. Used at a concentration of 2 mg/ml, its penetration was better after epithelial scraping[87,88].

FCZ is less effective than other drugs in the treatment of fungal endophthalmitis. Despite its good vitreal penetration when administered orally, its ineffectiveness against filamentous fungi discourage its use as an adjuvant. However, there are reports of successful treatment of endogenous endophthalmitis by *Candida* spp. with FCZ[89-91].

Even though its ocular penetration is superior to KCZ, in vitro and in vivo studies showed that the antifungal spectrum of FCZ is narrower. In several studies that evaluated the susceptibility of causative agents of fungal keratitis and endophthalmitis, only *Candida* species were susceptible to FCZ, and filamentous fungi (*Aspergillus* and *Fusarium* spp.) exhibited marked resistance[34,48,77,92].

- Voriconazole

VCZ has the same mechanism of action than first-generation triazoles, but is more effective in blocking the synthesis of ergosterol. VCZ was developed from the FCZ molecule and presents better efficacy at lower MICs than the first triazoles, which increases its effectiveness against filamentous fungi[8]. Because of its great efficacy in treating disseminated fungal infections, with lower toxicity compared to AMB, VCZ is currently the drug of choice in the treatment of invasive aspergillosis[93].

VCZ is commercially available for oral and parenteral administration (Vfend™ - Pfizer, New York, NY). It is metabolised by the liver, therefore liver enzymes should be controlled during therapy. Among its side effects are visual disorders (blurred vision, change in colour perception and photophobia), which are present in about 30% of patients using the drug and are usually reversible. Similar to FCZ, it presents good gastric absorption and bioavailability[4,92].

Administered orally at a dose of 200 mg every 12 hours, VCZ reaches peak plasma concentrations after 2-3 hours. The drug has been extensively studied in the treatment of keratitis and endophthalmitis due to its good concentrations in several ocular tissues (cornea, vitreous and aqueous)[32,94]. Hariprasad et al. found concentrations of VCZ in the vitreous and aqueous humours corresponding to 38% and 51% of plasma levels, respectively, after oral administration. Although the concentrations achieved in the vitreous were insufficient to treat infections by *Fusarium* spp., the authors argue that the study was conducted in non-inflamed eyes, and that in the presence of inflammation a more permeable blood-ocular barrier would help increase the local concentrations of the drug[95]. Alfonso et al. suggest VCZ as the drug of choice for oral use in the treatment of deep keratitis, scleritis, and endophthalmitis and as prophylaxis after penetrating keratoplasty[2]. Hariprasad et al. also suggest oral VCZ as prophylaxis in cases of ocular trauma with plant material[92].

Intravitreal administration was shown to be safe in an experimental model with rats, with no changes in electroretinography in doses up to 25mg/ml[96].

There are also numerous reports of therapeutic success with topical VCZ. Administered at a concentration of 1 mg/ml, it

was effective in the treatment of keratitis by *Candida*, *Aspergillus*, *Fusarium*, *Scedosporium*, and *Paecilomyces*, among others[97-101]. Its advantages compared to polyenes include its greater stability to light and temperature, remaining effective for up to 30 days[102,103]. Studies in horses showed drug penetration even with epithelial integrity[104].

Some reports support the use of intracorneal VCZ in cases of deep keratitis unresponsive to topical and/or oral administration. Prakash et al. report success in three cases of keratitis unresponsive to topical NTM using VCZ 50 ìg/0.1 ml[105]. Recently Siatiri et al. described 3 cases of *Fusarium* keratitis unresponsive to topical treatment that resolved after intracorneal VCZ[106]. The authors suggest that direct injection of VCZ in the cornea increases its concentration above its minimum inhibitory concentration for *Fusarium* species. Sharma et al., in a series with 13 patients, also suggest the use of intrastromal VCZ in refractory keratitis[107].

However, there are few studies comparing VCZ with other antifungal agents. In a multicenter randomised study VCZ was not found to be superior to NTM, with both groups having similar healing times and final visual acuity[41]. There are even reports of treatment failure with VCZ. Giaconi et al. reported two cases, a keratitis by *Fusarium oxysporum* and another by *Colletotrichum dematium*, which were unresponsive to topical therapy with VCZ[108].

In vitro studies demonstrate the superiority of VCZ to AMB against *Aspergillus* spp.[109-112]. Against *Fusarium* species, the absolute MIC of VCZ, NTM and AMB were similar, with VCZ having a lower relative MIC than the polyenes[47]. Even so, the minimum inhibitory concentration of VCZ for *Fusarium* species was superior to *Candida* and *Aspergillus* species[77].

- Posaconazole

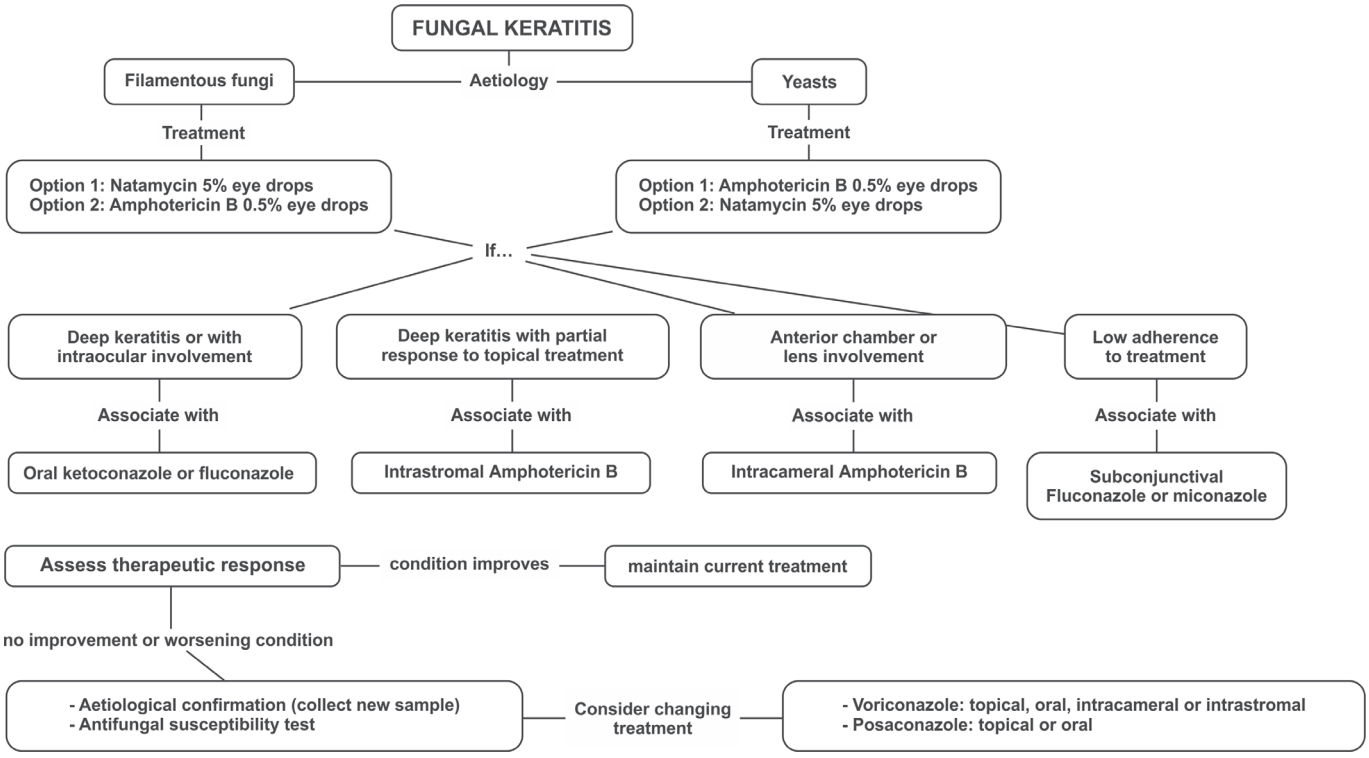
Similar to VCZ, PCZ is a second-generation triazole recently introduced into medical practice. It results from an improvement in the molecule of ICZ and is primarily indicated for the treatment of invasive fungal infections in onco-hematological patients. It is only available as an oral solution (Noxafil™ - Schering-Plough, Kenilworth, NJ) and should be administered at a dose of 200 mg four times daily or 400 mg twice daily. A parenteral presentation is currently being developed. Gastrointestinal complaints are the

Table 1

Antifungal agents and their indications

Drug	Route of administration	Dosing	Indication
Amphotericin B	Topical	1.5-5mg/ml	- First choice in the treatment of keratitis by yeasts - Alternative to NTM in the treatment of keratitis by filamentous fungi
	Intrastromal	5-10µg	- Deep keratitis with partial response to topical treatment
	Intracameral	5-10µg/0.1ml	- Keratitis affecting the internal chamber and/or lens
	Intravitreal	1-10µg/0.1ml	- First choice in the treatment of fungal endophthalmitis (by yeasts or filamentous fungi)
Natamycin	Topical	50mg/ml	- First choice in the treatment of fungal keratitis by filamentous fungi - Alternative to AMB in the treatment of keratitis by yeasts
Miconazole	Subconjunctival	1.2-10mg/1ml	- Associated with topical therapy in patients with low adherence to treatment
Econazole	Topical	20mg/ml	- Alternative to NTM in keratitis by filamentous fungi
Ketoconazole	Oral	100-400mg every 12h	- Associated with topical therapy in deep keratitis or those affecting intraocular tissues
Itraconazole	Oral	400mg/day	- Associated with topical therapy in deep keratitis by yeasts or those affecting intraocular tissues
Fluconazole	Topical	2mg/ml	- Alternative to polyenes in the treatment of fungal keratitis
	Subconjunctival	2mg/1ml	- Associated with topical therapy in patients with low adherence to treatment
	Oral	200-400mg/day	- Associated with topical therapy in deep keratitis or those affecting intraocular tissues
Voriconazole	Topical	1mg/ml	- Fungal keratitis resistant to polyenes and first-line triazoles
	Intrastromal	50µg/0,1ml	- Deep keratitis with partial response to topical drugs or in patients with low adherence to treatment
	Intracameral	50µg/0,1ml	- Fungal keratitis affecting the internal chamber and/or lens
	Intravitreal	50µg/0,1ml	- Alternative to AMB in fungal endophthalmitis
	Oral	200mg every 12h	- Associated with topical therapy in deep keratitis or those affecting intraocular tissues- Prophylaxis after eye trauma with plant material
Posaconazole	Topical	100mg/ml	- Fungal keratitis resistant to polyenes and first-line triazoles
	Oral	200mg every 6h or 400mg every 12h	- Adjunctive therapy in deep keratitis and endophthalmitis by organisms resistant to polyenes and first-line triazoles.
Flucytosine	Topical	10mg/ml	- Associated with topical AMB in fungal keratitis by yeasts
Caspofungin	Topical	1.5-5mg/ml	- Fungal keratitis by yeasts resistant to polyenes and first-line triazoles
Micafungin	Topical	1mg/ml	- Fungal keratitis by yeasts resistant to polyenes and first-line triazoles

Figure 1. Treatment algorithm for fungal keratitis



only adverse effects reported to date[113].

In vitro and in vivo studies show that PCZ has a broad spectrum against *Candida* spp., *Cryptococcus neoformans*, *Aspergillus* spp., and *Fusarium* spp., among others. PCZ was effective against most agents resistant to ICZ and FCZ[114,115] and, together with VCZ, had the lowest MIC against multiple agents[47].

Experience with its use in ocular infections is still limited, but initial results are encouraging. In a series of three cases of *Fusarium* keratitis progressing to endophthalmitis unresponsive to treatment with oral and topical VCZ, a rapid therapeutic response to PCZ was observed[36]. Sponsel et al. also describe a case of keratitis by *Fusarium solani* resistant to AMB and NTM but successfully treated with oral PCZ 200 mg 4 times daily associated with topical use (100 mg/ml prepared from an oral solution)[116]. However, comparative controlled studies with first-line antifungal agents are still lacking.

PYRIMIDINES

Pyrimidines are represented by 5-fluorocytosine (5-FC) or flucytosine, which is the only antifungal agent with intracellular action. After being absorbed by the fungus it is converted into 5-fluorouracil, a powerful antimetabolic which acts by inhibiting the synthesis of DNA[4,117].

Its use in eye infections is restricted due to its narrow antifungal spectrum and low penetration into ocular tissues[17]. It is effective against *Candida* spp., with varied action against *Aspergillus* spp. It is ineffective against *Fusarium* spp. Systemic or topical administration should be associated with AMB, primarily due to its potentiating effect (synergism) and because of induction of resistance when 5FC is used alone[4,6,77,118].

ECHINOCANDINS

Echinocandins are semisynthetic lipopeptides that inhibit the synthesis of glucan in the fungal cell wall through non-competitive inhibition of the enzyme 1,3-â-glucan synthase, causing osmotic imbalance and cell lysis[8,119,120]. This class of drugs includes caspofungin (CFG) and micafungin (MFG).

Used in yeast infections, echinocandins have rapid fungicidal action against most *Candida* species, including strains resistant to FCZ, but not against *Cryptococcus*, *Rhodotorula* and *Trichosporon*[121]. Echinocandins have fungistatic action against some filamentous fungi such as *Aspergillus*, but not against *Fusarium* and *Rhizopus*[47,122]. CFG is administered intravenously (Cancidas™ - Merck & Co - Whitehouse Station, NJ) at a dose of 70 mg on the first day and 50 mg on the following days[4,8]. MFG (Mycamine™ - Astellas Ireland - Killorglin, Ireland) is also administered intravenously at a dose of 100 to 150 mg/day.

Topical CFG at a concentration 1.5 to 5 mg/ml was as effective as AMB in the treatment of corneal ulcer by *Candida albicans* in an animal model[123]. Two other studies involving topical MFG 1 mg/ml found an efficacy comparable or superior to FCZ in the treatment of keratitis by *Candida albicans* and *Candida parapsilosis*[124,125].

ASSOCIATION OF ANTIFUNGAL AGENTS

In order to increase treatment efficiency or even broaden the antifungal spectrum, drugs are commonly associated in the treatment of eye infections. Although some combinations of antifungals such as 5-FC and AMB are widely used[126], other less studied associations may not be as effective as expected.

Azoles are often associated with standard topical antifungal agents such as NTM or AMB. However, several studies

showed an antagonistic effect between these drugs. The introduction of an azole decreases the synthesis of ergosterol in the cell membrane, a binding site for polyenes, whose action is therefore decreased.

Arora et al. observed this antagonistic effect between ECZ and AMB in the treatment of fungal keratitis, whose association produced therapeutic results similar to ECZ alone[127]. In a review article, Sugar et al. showed an in vitro antagonistic effect between AMB and various azoles (MCZ, KCZ, FCZ and ICZ), with decreased polyene action[128]. In a similar study, Li et al. found an antagonistic effect between NTM+ICZ and NTM+FCZ and a synergistic effect between AMB+ICZ[48].

Studies in humans and animals usually do not reproduce these laboratory findings. There are countless reports of improvement with the association of antifungal agents, especially when topical AMB is associated with first- and second-generation systemic triazoles[129,130]. This combination should be used in deep corneal infections or those with intraocular involvement.

The combination of two drugs of the same class is discouraged (e.g. NTM+AMB) because it increases local toxicity and also fails to increase therapeutic efficacy[131].

OTHER DRUGS

Alternatives to antifungal agents have been studied to treat keratitis of unclear aetiology. In a number of cases, povidone-iodine 2.3% was used successfully to treat keratitis by *Candida albicans* and *Acremonium strictum*[132]. However, in a comparative study, povidone-iodine 0.5% showed no benefit compared to NTM 5% in the treatment of experimental keratitis by *Fusarium solani*[40]. In another experimental study, Fiscella et al. showed that polyhexamethylene biguanide (PHBM) 0.02% is effective in the treatment of eye infections by *Fusarium solani* in rabbits[133]. However, there are no comparative studies between PHMB and antifungal agents.

Experimental trials involving topical corticosteroids associated with antifungal therapy found deleterious effects. O'Day et al. showed a modified host response after the introduction of corticosteroids. In their study, in rabbits infected with *Candida albicans*, *Aspergillus fumigatus* and *Fusarium solani* that received subconjunctival corticosteroids corneal sterilisation occurred later than in the control group[134]. Weiyun et al. studied the risk factors for recurrence of the fungal infection after transplantation and found a six-fold increase in the risk of recurrence in patients who received topical steroids prior to transplantation[135].

Conclusion

There are many options of antifungal agents and routes of administration, and the choice depends on both the aetiologic agent and the location and extent of the infection (Table 1).

Standard therapy with polyenes remains effective. Despite the numerous reports of infections that do not respond to first-line drugs and improve after the introduction of other agents, particularly second-generation triazoles, comparative studies demonstrating the superiority of the latter are lacking.

Until the real benefit of the new generation of antifungal agents is demonstrated, we believe such drugs should be used as an alternative to standard therapy (Figure 1).

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